# Role of magnesium in post thyroidectomy hypocalcemia

A dissertation submitted in partial fulfilment of the requirements of M.Ch Endocrine Surgery (Branch - IX) examination of the Tamil Nadu Dr. MGR Medical University, Chennai to be held in August 2014.

# Certificate

This is to certify that the dissertation entitled “Role of magnesium in post thyroidectomy hypocalcemia” is a bonafide work done by Anish Jacob Cherian, M.Ch registrar in Endocrine Surgery at Christian Medical College, Vellore in partial fulfilment of the University rules and regulations for award of M.Ch Endocrine Surgery under my guidance and supervision during the academic year 2011 to 2014

Name & Signature

| | |
|---|---|
| Guide and Head of the Department | Principal |
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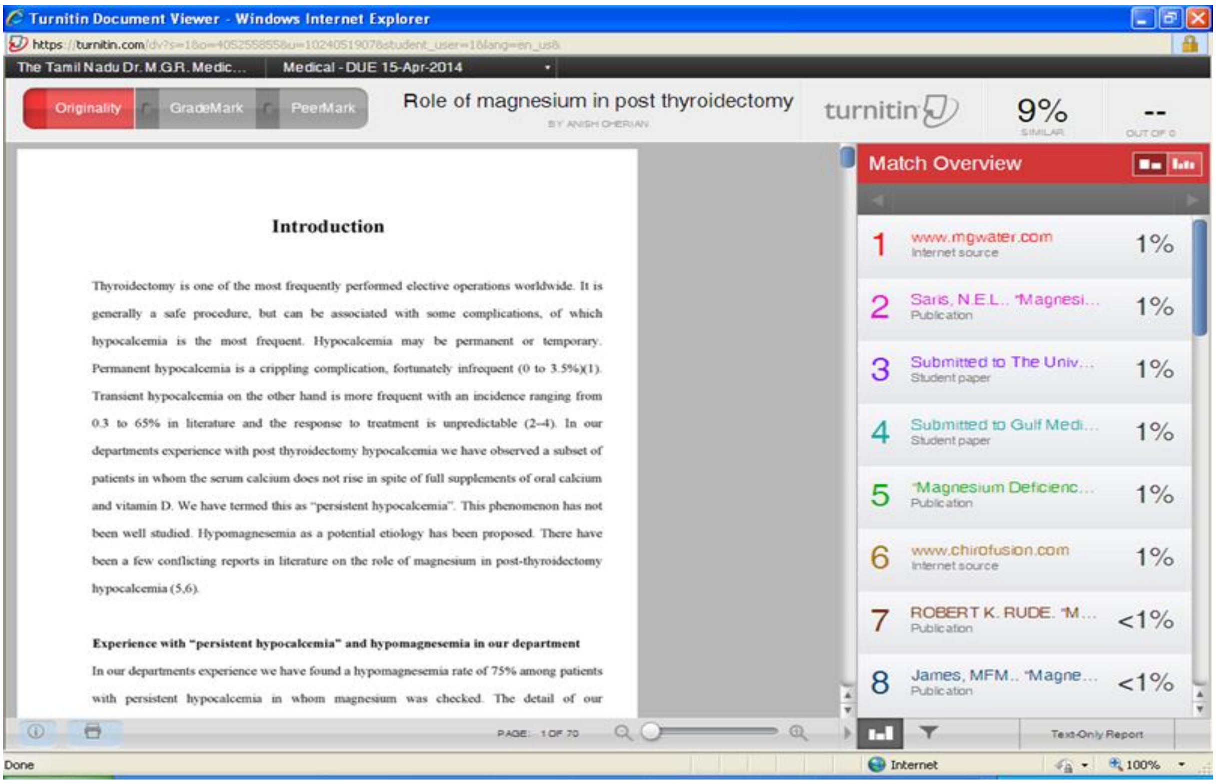
# Plagiarism online checker

# IRB approval letter

Ref: IRB Min. No. 7882 dated 27.06.2012

Dear Dr. Cherian,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Role of magnesium in post thyroidectomy hypocalcaemia" on June 27, 2012. I am quoting below the minutes of the meeting.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Proforma
3. Patient Information and Consent Form (English)
4. Cvs of Drs. MJ Paul, Deepak Abraham, Pooja Ramakant, Thomas V Paul.
5. A CD containing documents 1 - 4

We approve the project to be conducted as presented.

The Institutional Review Board expects to be informed about the progress annually of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

Administrative committee's approval is to be obtained for opening the account-head, employing any personnel or purchasing any equipment. The investigator also needs to present to Administrative Committee, the terms and condition of the Funding agency for approval.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Secretary

# Acknowledgments

I would like to thank the Dr. MGR medical university for giving me this opportunity to conduct a thesis.

I am grateful to the patients who consented to be part of this study.

I was very privileged to have Dr. MJ Paul as my guide. I thank him for teaching me the process of doing a thesis. I thank him for his guidance and support. Without his persistence, gentle reminders and deadlines set for me I would not have completed this on time.

I would like to specially thank Dr. Aravindan Nair for his expert opinions and suggestions.

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Abstract

**Title of the abstract:** Role of magnesium in postthyroidectomy hypocalcemia

**Department:** Endocrine surgery

**Name of the candidate:** Anish Jacob Cherian

**Degree and subject:** Mch Endocrine Surgery

**Name of the guide:** Prof. MJ Paul

**Key words:** Magnesium, hypomagnesemia, hypocalcemia, total thyroidectomy, thyroidectomy complications

## Aim and objectives:

The aim of the study was to evaluate the role of magnesium in postthyroidectomy hypocalcemia. The objectives were to:

A) Estimate the prevalence of hypomagnesemia in patients undergoing thyroidectomy and in post thyroidectomy patients and its relationship with hypocalcemia

B) Evaluate the relationship of the following factors to post thyroidectomy hypocalcemia: Age, gender, vitamin D level, thyrotoxicosis, inadvertent parathyroid injury/removal, hemodilution, extent of dissection and duration of operation

## Material and methods:

This was a prospective observational study conducted from 1st October 2012 to 30th September 2013 at the department of Endocrine Surgery, Christian Medical College,

Vellore, India. The sample size was 50. The statistical analysis was performed using STATA I/C 10.1. This study was approved by the institution review board.

## Results:

Majority of the patients (26%) were in the fifth decade. A female predominance was noted. Seventy four percent of the patients had carcinoma thyroid, the most common malignancy being papillary carcinoma thyroid. Seventy two percent underwent total thyroidectomy. The prevalence of hypomagnesemia preoperatively was 24% and following thyroidectomy this increased to 70% percent. Hypovitaminosis D was prevalent (62%). Postoperative hypocalcemia was seen in fifteen patients (30%). We found a similar trend of the fall and gradual normalization of calcium and magnesium postoperatively though there was no significant association between the two. There was a significant direct correlation between amount of fluids used and development of hypocalcemia ($p=0.04$) and low PTH (<8pg/ml) with postoperative hypocalcemia ($p=0.029$). There seemed to be a protective effect of hypovitaminosis D for hypocalcemia. Age of the patient, gender, presence of thyrotoxicosis and duration of operation had no bearing on the postoperative hypocalcemia in our study.

## Conclusions:

1) The prevalence of hypomagnesemia is 24% preoperatively in this cohort of patients. They were all mild deficiency 1.6 to 1.8. Vitamin D deficiency (< 20) was 62%.
2) The postoperative hypocalcemia (calcium <8mg/dl) rate was 30%. Hypovitaminosis D appeared to protect against postoperative hypocalcemia; this finding is at variance with published literature.

3) There was a marked rise in postoperative hypomagnesemia (70%). A similar pattern of fall in calcium and magnesium following thyroid surgery which normalized by one to two weeks without intravenous correction was observed.
4) Hemodilution and low PTH were significantly associated with post thyroidectomy hypocalcemia. The ROC curve showed that a PTH of 4.1-6pg/ml was the best predictor of hypocalcemia.
5) The cause of hypocalcemia post thyroidectomy in this study is mainly a factor of parathyroid function and fluid status. Magnesium levels tend to mimic the calcium levels postoperatively and there is possibly an association rather than a causation. This study therefore does not prove or disprove the role of magnesium supplementation to help correct postoperative hypocalcemia.

# Introduction

Thyroidectomy is one of the most frequently performed elective operations worldwide. It is generally a safe procedure, but can be associated with some complications, of which hypocalcemia is the most frequent. Hypocalcemia may be permanent or temporary. Permanent hypocalcemia is a crippling complication, fortunately infrequent (0 to 3.5%)(1). Transient hypocalcemia on the other hand is more frequent with an incidence ranging from 0.3 to 65% in literature and the response to treatment is unpredictable (2–4). In our experience with post thyroidectomy hypocalcemia we have observed a subset of patients in whom the serum calcium does not rise in spite of full supplements of oral calcium and vitamin D. We have termed this as “persistent hypocalcemia”. This phenomenon has not been well studied, Wilson et al experienced that “hypomagnesemia occurs after total thyroidectomy and if untreated, particularly in the presence of hypocalcemia, may lead to persistent symptoms” (5). Hypomagnesemia as a potential etiology has been proposed.

**Our experience with “persistent hypocalcemia” and hypomagnesemia**

In our experience we have found a hypomagnesemia rate of 75% among patients with persistent hypocalcemia in whom magnesium was checked. The detail of our observation is depicted in the flow charts below.

**Figure1: Depicting the patients who developed hypocalcemia and "persistent hypocalcemia" in a two year period**

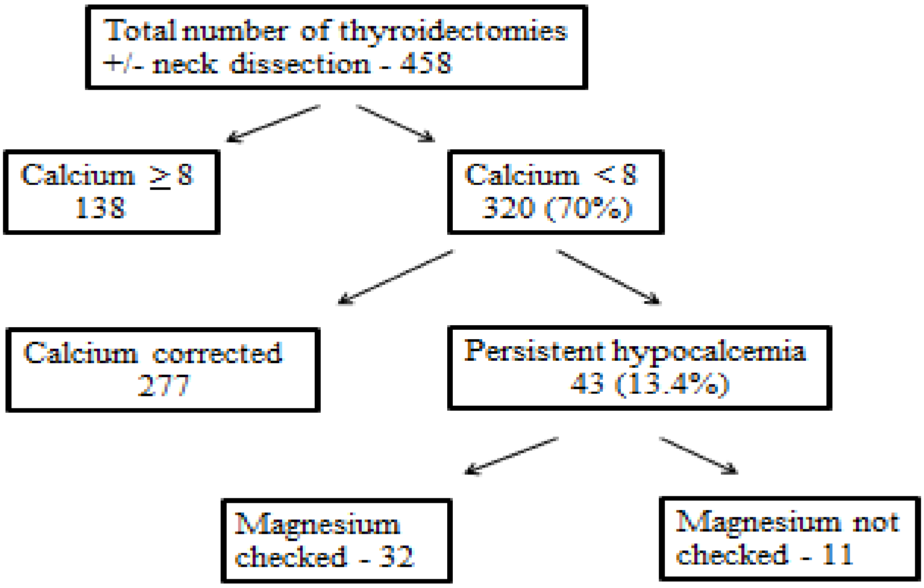
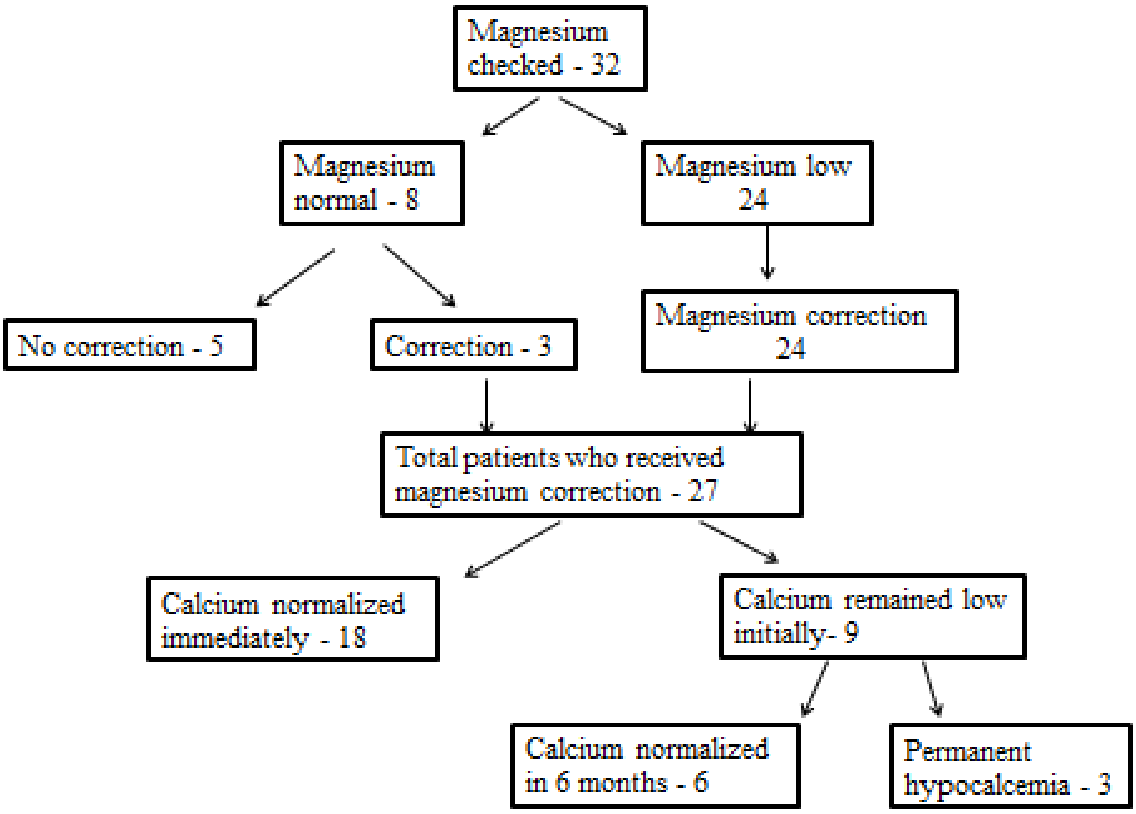



**Figure 2: Depicting the relationship of magnesium with hypocalcemia in the "persistent hypocalcemia" subset of patients**



Nineteen out of thirty two patients (60%) were at increased risk of developing persistent hypocalcemia postoperatively. The risk factors for the development of hypocalcemia postoperatively in these patients included extended surgery (central compartment clearance +/- lateral neck dissection) – 9 patients, toxic goitre – 3 patients, locally infiltrative thyroid – 3 patients, low PTH post operatively – 3 patients and retrosternal goitre – 1 patient.

Our department policy is to check magnesium levels in patients with “persistent hypocalcemia”. In three patients with “persistent hypocalcemia”, following sample collection for magnesium, intravenous magnesium was administered. Later their magnesium level was found to be within the reference range. Hence three patients received magnesium though they were normomagnesemic.

A possible role of magnesium in the correction of hypocalcemia among the “persistent hypocalcemia” patients was observed in eighteen out of twenty seven patients (66.7%).

Therefore we prospectively studied the role of hypomagnesemia in post thyroidectomy patients and its relationship with hypocalcemia. We also evaluate the other risk factors for post thyroidectomy hypocalcemia documented in literature.

# Aim and objectives

A) To evaluate the role of magnesium in post thyroidectomy hypocalcemia

B) To estimate the prevalence of hypomagnesemia in

   a. Patients undergoing thyroidectomy

   b. Post thyroidectomy patients and its relationship with hypocalcemia

C) To evaluate the relationship of the following factors to post thyroidectomy hypocalcemia:

1) Age
2) Gender
3) Vitamin D level
4) Thyrotoxicosis
5) Inadvertent parathyroid injury/removal
6) Hemodilution
7) Extent of dissection
8) Duration of operation

# Review of literature

Thyroid disorders are common the world over. It has been estimated that about 42 million people in India suffer from thyroid disease (6). Thyroidectomy is one of the most frequently performed operations in India. It is associated with many complications, hypocalcemia being the most common (7).

## Definition of hypocalcemia

There is a lack of consensus on the definition of post thyroidectomy hypocalcemia in literature. The definition differs in (8)

1) The calcium cutoff point

Literature is divided on the calcium level to be taken as the cutoff point to define hypocalcemia. Some authors have used the lower limit of their laboratory reference range for calcium as the cutoff point (9–12). Others have used a calcium value below the lower limit of their laboratories reference range <7mg/dl (13,14). The most commonly used cutoff point was calcium <8mg/dl (15–19).

2) Inclusion criteria

Opinion is also divided in literature regarding including patients depending on the presence or absence of symptoms of hypocalcemia (9,13,20–22). Some authors have further complicated this issue by considering those whom require calcium supplements following thyroidectomy to maintain calcium level within reference range or to eliminate clinical symptoms of hypocalcemia or both, within the definition of post thyroidectomy hypocalcemia (9,20).

3) Duration of hypocalcemia

Finally, the duration of hypocalcemia to distinguish temporary from permanent hypocalcemia is also mixed in literature. Reported durations considered are two months, six months and one year (12,20,23). Hence the reported rate of transient hypocalcemia varies from 0.3 – 65%(2–4). There is agreement that considering less than two months as a cutoff point to define temporary hypocalcemia is too short a period as we need to give time for patients with thyrotoxicosis to recover from hungry bone syndrome.

The cause of post thyroidectomy hypocalcemia is multifactorial. Parathyroid removal, injury or devascularization, are the main causes. Other factors proposed include age, female gender, vitamin D level, thyrotoxicosis, extent of operation, hemodilution, magnesium level and calcitonin(4,14,24–29).

## Physiology of magnesium

Until recently, the function of magnesium in the biological process was largely ignored to the point where it was described as the "forgotten ion"(30). In recent years there has been an explosion of interest in the physiological and therapeutic properties of this ion.

## Tissue distribution of magnesium

Magnesium is the fourth most abundant cation in the body. The human body contains about 21-28 g of magnesium (31). Of the body's magnesium, 60% is found in the bone, 30-40% in muscle and soft tissue and approximately 1% in blood plasma and red blood corpuscles (extracellular) (32). In the extracellular compartment magnesium is distributed as follows, 70-

80% in the ionized form, 20-30% protein bound non-ultrafilterable and 1-2% complex bound (31). As is evident magnesium is present mainly in the intracellular compartment being the second most abundant cation here (33). Within the cell most of the magnesium lies within the mitochondria.

It is observed that in people who have albumin levels out of normal reference range, albumin and magnesium concentrations follow a linear pattern of relationship. Whereas when albumin is within reference range, magnesium concentrations are independent of albumin concentrations (33).

## Laboratory measurement of total magnesium

Biochemical assays used to measure the total magnesium are

1) Photometry
2) Atomic spectroscopy
3) Inductively coupled plasma
4) Optical emission

Among these the photometric assay is the simplest, easiest to perform, least expensive and the most commonly employed method. Our laboratory uses this method.

## Functions of magnesium

Magnesium is required in many processes in the body. These include (31):

1) Functioning as a cofactor in enzymatic reactions

Adenylate cyclase, sodium-potassium-adenosine triphosphate (Na-K-ATPase), carboxylase, transketolase, ribonuclease and kinase are enzymes that are dependent on magnesium.

The mechanisms by which magnesium acts as a cofactor are (34):

a) Binding to ligands such as ATP in "ATP requiring enzymes"

b) Binding to the active site of the enzyme

c) Causing a conformational change during the catalytic process

d) Promoting the aggregation of multi-enzyme complexes

e) Mixture of the above mechanisms

2) Aiding in the metabolism of fat and carbohydrate to produce energy

Magnesium is necessary for the activation of enzymes required for carbohydrate (glucokinase, hexokinase, galactokinase, phosphorylase phosphatase, phosphorylase kinase etc.) and lipid metabolism (acetylcoenzyme A synthetase, acylco A synthetase, beta-ketothiolase, diglyceride kinase etc.) hence helps in producing energy.

3) Synthesis and utilization of energy rich compounds

The energy necessary for functioning of the cell is stored in the form of energy-rich bonds, the phosphoric anhydride bond that is found mainly in ATP, GTP (guanosine triphosphate), UTP (uridine triphosphate), CTP (cytosine triphosphate) and ITP (inosine triphosphate). Magnesium is necessary for the synthesis of various compounds that have energy-rich bonds. Magnesium has also been established as necessary for the utilization of energy-rich bonds by activating all reactions that transfer the phosphorylated radical.

4) Necessary for protein and nucleic acid synthesis

Magnesium is required for the function of the enzymes of nucleic acid and protein metabolism, RNA polymerase (which allows the synthesis of RNA and especially that of messenger RNA) and DNA polymerase which allows the reconstitution and recombination of DNA. Magnesium is also necessary for the physical integrity of the double helix of DNA.

5) Provides cytoskeletal and mitochondrial integrity

Phospholipids form complexes with magnesium as well as with calcium, which explains why magnesium is an integral part of the structure of many membranes (cellular or subcellular, plasma or mitochondrial, reticular and sarcoplasmic); this ensures proper nerve and muscle function.

6) Helps modulate immunological functions such as granulocyte oxidative burst, lymphocyte proliferation and endotoxin binding to monocytes (35).

## Absorption and excretion

**a) Absorption**

Absorption of magnesium takes place mainly in the ileum and colon. The process of magnesium absorption is via paracellular and epithelial pathways (31).

**b) Excretion**

Excretion of magnesium occurs at the kidney. Seventy five percent of the total plasma magnesium is filtered in the glomerular membrane. Only 3-5% of the filtered magnesium is excreted in the urine, the remaining being reabsorbed in the proximal tubule and the ascending loop of Henle (31).

## Regulation of cellular availability of magnesium

The availability of magnesium is closely regulated by the kidney, gastrointestinal tract and the bone as evidenced above. Minor contributions to regulating availability of magnesium are provided by (31):

1) Calciotropic hormones –

a) PTH - i) Stimulates magnesium reabsorption at the loop of Henle and distal tubule.

ii) Releases magnesium from bone

iii) Increases magnesium reabsorption from the small intestine

These actions of PTH are mediated by adenylate cyclase and production of cAMP.

b) Vitamin D – increases intestinal absorption of magnesium through active transport.

c) Calcitonin – has been reported to stimulate renal magnesium reabsorption in rat. It activates adenylate cyclase at different parts of the nephron than PTH.

2) Alpha and beta adrenergic agonists – Both these agonists stimulate magnesium efflux in cardiac and liver cells.

3) Vasopressin – Causes accumulation of magnesium in cardiac myocytes.

4) Estrogen and progesterone – At ovulation it is observed that ionized magnesium levels are reduced, whereas total magnesium level is reduced during luteal phase. This indicates a role of estrogen and progesterone in magnesium homeostasis.Estrogen has been seen to be inhibitory to PTH induced bone resorption.

5) Insulin – Several studies have shown that the frequency of hypomagnesemia among diabetic patients is higher than expected. Hypomagnesemia correlated with the severity of hyperglycemia. It has been postulated that insulin may enhance magnesium uptake at the cells, and also cause a decrease excretion of magnesium.

6) Glucagon – The action of glucagon is via adenylate cyclase resulting in an increased resorption of magnesium at the loop of Henle and distal convoluted tubule.

## Sources and daily requirements of magnesium

Rich sources of magnesium in the diet include whole seeds, unmilled grains, green leafy vegetables, legumes, shellfish and nuts. Fish, meat, milk and fruits are poor sources of magnesium(31,32). The WHO (World Health Organization) recommended daily intake of magnesium for adult men is 260mg/d and for adult woman 220mg/d (32).

## Hypomagnesemia

The development of hypomagnesemia is rare as most people have large stores of magnesium in their body. It may develop as a result of either a disturbance in intestinal magnesium absorption or an increased renal excretion of magnesium.

Disturbance in intestinal absorption of magnesium is due to the formation of nonabsorbable fatty acid soaps in conditions such as malabsorption, steatorrhea and chronic pancreatic insufficiency. Other causes related to intestinal absorption include severe diarrhea, chronic/severe vomiting and resection of large volume of intestine.

Patients with poorly controlled diabetes, those with kidney disease, those who are chronic alcohol consumers and certain drugs such as thiazide diuretics, cisplatin, gentamicin and cyclosporine cause an increased renal excretion of magnesium resulting in hypomagnesemia(31,36).

Endocrine related causes of magnesium deficiency include primary hyperparathyroidism (PHPT) and hyperthyroidism. Magnesium reabsorption in the kidney is linked to calcium. Hence hypomagnesemia in PHPT patients is probably related to the effect of calcium on renal handling of magnesium. Thyrotoxic patients have a decreased serum magnesium concentration along with increased urinary magnesium excretion (37).

The chronic usage of proton pump inhibitors (PPI) has been shown to result in hypomagnesemia (38–41). PPI's impair absorption of magnesium by the intestinal epithelial cells by inducing inhibition of transient receptor potential melastatin 6 and 7 channels (42).

## Prevalence of hypomagnesemia

One of the reasons for a recent increased interest in magnesium among clinicians is because of reports of high prevalence of hypomagnesemia among patients admitted to the intensive care units (ICU). In these patients it was observed that their mortality rates were higher compared to patients who were normomagnesemic. Hence there has been extensive literature on hypomagnesemia among ICU patients documented in literature. Magnesium affects the smooth muscle vasoconstriction and this is implied in the pathophysiology of severe critical illness. Hypomagnesemia is known to cause muscle weakness and respiratory failure and magnesium is proposed to play a role in sepsis. These factors contribute to the increased mortality seen among hypomagnesemic patients who are critically ill. The prevalence of hypomagnesemia among critically ill patients documented vary between 20-65%(35,43–46).
The prevalence of hypomagnesemia in the general population has not been well documented. Published data on the prevalence in Iranian and German populations range from 4.6%-14.5% (47,48). In India the only record of prevalence of hypomagnesemia in the general population is limited to pregnant women in a rural community of Haryana – 43.6% (49).

## **Conditions associated with hypomagnesemia** (31)

1) Ischemic heart disease - Hypomagnesemia has been found to induce severe vascular damage in the heart and kidneys. It causes vasoconstriction of coronary

arteries, induces myocyte aggregation, accelerates development of atherosclerosis and leads to hypertension.

2) Atherosclerosis
3) Stroke - Magnesium is neuroprotective. Its mechanism of actions are non-competitive block of NMDA (N-methyl-D-aspartate) receptors, increased regional cerebral blood flow to ischemic areas and a decrease in entry of calcium into the cells through leak.
4) Preeclampsia/Eclampsia
5) Hypertension - Supplementation of magnesium has shown to cause a decrease in blood pressures in several studies.
6) Diabetes mellitus - There is a strong relationship between magnesium and diabetes. Hypomagnesemia increases the insulin resistance and inclines patients to cardiovascular diseases. Studies have shown that oral supplementation of magnesium has resulted in better control of diabetes.

## Clinical features of hypomagnesemia

The symptoms of hypomagnesemia include anorexia, nausea, vomiting, dysphagia, lethargy, weakness, paresthesia, muscular cramps, tetany, irritability, decreased attention span, mental confusion, cardiac arrhythmias and pulmonary edema(31,37,50).

The most common symptoms are neuromuscular. The neuromuscular symptoms develop because magnesium stabilizes the axon and affects the release of neurotransmitters at the myoneural junction. In patients with hypomagnesemia there is

a) A lower threshold for axonal stimulation

b) Increased nerve conduction velocity

c) Increased quantity of neurotransmitters released

d) Calcium is more readily released from the sarcoplasmic reticulum and is reaccumulated more slowly.

This results in a muscle that is readily contractible to a given stimulus and is less able to recover from contraction – tetany prone (50).

The electrocardiographic (ECG) changes seen in magnesium depleted patients include prolonged P-R and Q-T interval and flat, broad T waves.

Positive Chvostek's and Trousseau's sign may also be elicited.

## Electrolyte imbalances resulting from magnesium deficiency

### a) Hypocalcemia

Hypomagnesemia has been associated with hypocalcemia in chronic disease states. Hypomagnesemia post thyroidectomy has not been studied extensively. Postulated theories of hypomagnesemia – hypocalcemia relationship include:

i) decreased production/secretion of PTH (50–54)

ii) end organ resistance to PTH (52,55,56)

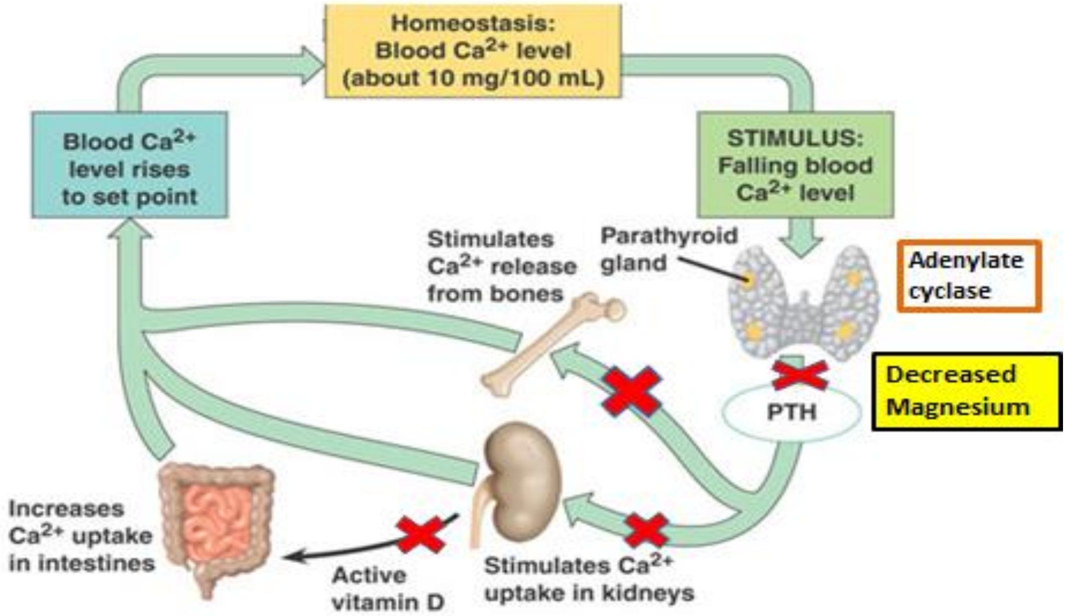
iii) decreased production of vitamin D (50,51,54)

Impaired PTH secretion is the most important element responsible for the hypocalcemia seen among patients who are hypomagnesemic. When hypomagnesemia occurs, initially the parathyroid gland responds normally with an increased PTH secretion. As intracellular magnesium is depleted, the ability to secrete PTH is progressively impaired. Defective PTH secretion is related to the decreased action of adenylate cyclase and phospholipase c enzymes. These enzymes are highly reliant on magnesium for their actions. Correction of the magnesium deficit has been shown to rapidly increase PTH secretion (within few minutes) and gradually increase serum calcium (30 min up to 3 days)(56–59). This also indicates a positive role of magnesium in hypocalcemia.

End organ resistance to PTH has been demonstrated in hypocalcemic-hypomagnesemia. Impaired generation of cyclic AMP in the kidney is responsible for renal resistance to PTH. The skeletal resistance to PTH could be due to decreased adenylate cyclase activity in this situation (37).

Vitamin D metabolism/action is disturbed in hypomagnesemia. This may be secondary to a decrease in PTH secretion or to a direct effect of magnesium depletion on the ability of the kidney to synthesize 1,25dihydroxivitamin D (50).

**Figure 3: depicting the hypomagnesemia – hypocalcemia relationship**



## Hypomagnesemic-hypocalcemia following total thyroidectomy

Two studies have evaluated the relationship of magnesium with post thyroidectomy hypocalcemia yielding contrasting results(5,60). Wilson et al have documented a transient fall in both calcium and magnesium following total thyroidectomy (5). In this study hypomagnesemia positively correlated with hypocalcemia and patients were more likely to become symptomatic when both cations were low. The other factors positively correlated with hypomagnesemia in their study were volume of intravenous fluids used and an associated neck dissection. Alexandre et al evaluated the changes in magnesium and phosphorous in patients undergoing total thyroidectomy and correlated it with calcium levels in the postoperative period (60). Their results showed a transient fall in magnesium levels post operatively. This fall was not below their reference range for magnesium. They did not find a statistical association between postoperative hypocalcemia and the fall in magnesium. They concluded that magnesium had no role in post thyroidectomy hypocalcemia.

Our own unpublished data has shown that patients who had persistent hypocalcemia, and in whom magnesium was checked, the majority of them had hypomagnesemia (75%). Correction of magnesium in this subset of patients appeared to aid in the correction of hypocalcemia in the majority.

**b) Hypokalemia**

Magnesium deficiency has been shown to affect the potassium homeostasis resulting in hypokalemia. The proposed etiologies are, a fall in intracellular potassium due to failure of the Na-K pump secondary to impaired Na-K ATPase which is magnesium dependent, and a lack of conservation of potassium by the kidneys during hypomagnesemia(35,37,50). In this situation as well it has been shown that the serum potassium cannot be corrected unless magnesium is corrected (35).

## Treatment of hypomagnesemia

Patients with mild to moderate hypomagnesemia (serum magnesium 1.2mg/dl-1.7mg/dl) should be treated with dietary/ oral magnesium supplements alone.

Symptomatic patients require slow intravenous magnesium sulphate upto 3-4g daily. Normal renal function needs to be documented prior to intravenous magnesium therapy. In patients who have renal dysfunction, 25-50% of the dosage may be administered.

Magnesium equilibrates slowly with the intracellular compartment and in hypocalcemic patients the calcium may take four to five days to return to normal(37,61).

## Other causes of post thyroidectomy hypocalcemia

Other factors influencing postoperative hypocalcemia are age, gender, vitamin D levels, thyrotoxicosis, extent and duration of the operation, inadvertent parathyroid injury/removal and hemodilution.

### 1) Age and gender

There is a controversy in literature regarding the effects of age and gender in the development of post thyroidectomy hypocalcemia. Some studies have shown that these two factors are not directly related (15), whereas other studies have shown a direct correlation between the two(24,25,62). In the last cited study, age above 50 was significantly correlated with post thyroidectomy hypocalcemia. The explanation provided being that elderly patients are at a higher risk of developing hypovitaminosis D which in turn leads to hypocalcemia

### 2) Vitamin D levels

It is postulated that patients with higher preoperative vitamin D levels are protected against hypocalcemia as these patients will be able to mobilize these reserves when there is an acute fall in PTH(3,24). Preoperative low vitamin D level (<15ng/ml) significantly correlating with post thyroidectomy hypocalcemia has also been demonstrated (62). Whereas, one study found no correlation between preoperative vitamin D levels and postoperative hypocalcemia (63).

Our own earlier unpublished data suggests a protective effect of low vitamin D to the development of post thyroidectomy hypocalcemia, which is contrary to the currently held view on their relationship in literature.

### 3) Thyrotoxicosis

Thyroxin causes resorption of calcium from the bones (64,65). Patients who are thyrotoxic have a large amount of circulating thyroxin. Following thyroidectomy, the bones of these patients being calcium deprived are hungry for calcium and hence take up all the circulating calcium leading to hypocalcemia. This phenomenon is referred to as hungry bone syndrome and has been proposed as one of the causes of post thyroidectomy hypocalcemia (66,67).

Alkaline phosphatase is an enzyme found in the osteoblast cells among other sites. It was introduced in 1929 as a biochemical marker of bone turnover (68). There are five specific forms of alkaline phosphatase: skeletal, hepatic, renal, intestinal and placental. Elevated alkaline phosphatase levels have been observed in thyrotoxic patients. It has been theorized that a similar elevation of alkaline phosphatase should be present in patients with vitamin D deficiency. This is due to secondary hyperparathyroidism. Two recent studies could not find a correlation between elevated alkaline phosphatase levels and hypovitaminosis D (69,70).

**4) Parathyroid status**

Preservation of all four parathyroid glands during thyroidectomy is ideal. The status of the parathyroid gland may be affected due to direct trauma to the gland, devascularization or inadvertent excision(26,28,71). This is the most common cause of post thyroidectomy hypocalcemia. Patients in whom a devascularized parathyroid gland has been identified during surgery, this gland may be autotransplanted into a neck muscle. These patients are prone to develop hypocalcemia in the postoperative period as an autotransplanted gland takes 6-8 weeks to regain function (71).

**5) Hemodilution**

A post thyroidectomy hypocalcemia-hypoproteinemia has been documented in previous studies. This has been confirmed by the similar evolution of other measured elements, suggesting that the hypocalcemia may be in part due to the transient postoperative hemodilution (15).

**6) Extent of dissection and duration of operation**

With regards to the extent of surgery, a positive correlation has been shown with total thyroidectomy when compared to less than total thyroidectomy. Other procedures with an increased risk include redo surgery, malignant thyroid disorders, retrosternal goitre and neck dissections(4,15,29). The reason for the hypocalcemia cited is the added risk of injury/devascularization to the parathyroid glands during these operations (71). Apart from this, hemodilution, as larger volumes of fluids would be administered for longer duration of surgery.

### 7) Weight of the thyroid gland

The size of the thyroid resected has been postulated to be a factor responsible for development of hypocalcemia after thyroidectomy (72–75). The alteration in structural anatomy, especially in the position of the parathyroid glands is the explanation given. Information regarding weight of the gland associated with hypocalcemia is limited in literature. The few reports indicate that a weight above 100g showed an increased risk of development of hypocalcemia (72,74). One report from Turkey had a conflicting result showing that weight below 50g being associated with hypocalcemia (75).

### 8) Calcitonin

A positive correlation between calcitonin and postoperative hypocalcemia secondary to a “calcitonin leak” that occurs during manipulation of the thyroid gland at surgery has been suggested in the past to cause post thyroidectomy hypocalcemia. Recent data does not support any such calcitonin leak – hypocalcemia correlation(15,76,77).

There are a few reports in literature depicting the evolution of calcium, magnesium and albumin in the postoperative period following thyroid surgery. The general trend seen was an early postoperative fall in these ions and a gradual normalization within one week (15).

All the above findings suggest that hypocalcemia is prevalent following thyroid surgery. The cause is probably multifactorial, iatrogenic parathyroid injury being the most common.

# Material and Methods

A prospective observational study was conducted from 1st October 2012 to 30th September 2013 at the department of Endocrine Surgery, Christian Medical College, Vellore, Tamil Nadu, India.

## Sample size

Literature on the role of magnesium on postoperative hypocalcemia is limited. Prevalence of hypomagnesemia in India has not been documented. Hence sample size could not be calculated using any formula. Estimating that our department performs about 5 thyroidectomies'/week, 20/month, 240/year, and anticipating one year data collection we chose 100 as our sample size. We were subsequently limited by funding and had to decrease sample size to a final 50.

Proforma for case record is appended below.

## Proforma

**1. Patient name**:
**2. Hospital number**:
**3. Age**: **4**. **Gender**: **5**. **Address**:
**6. Indication for surgery**:
**7. Preoperative**:
Signs of hypocalcemia – Chvostek +/-
**8. Biochemical tests**:
Preop:
Ca Alb Mg
P Vit D PTH Alk phos
**9. Operation performed**:

**10. Parathyroid status intraoperative**:

Number Seen
Number Preserved
Number Autotransplanted

**11. Duration of operation (in minutes)**:
**12. Volume of fluids used intraoperative (in ml):**
**13. Weight of thyroid gland:**

**14. Postoperative**:

a) Symptoms of hypocalcemia : +/-

| Day | Occasional tingling | Severe paresthesia | Mild cramps | Severe cramps |
|---|---|---|---|---|
| D1 | | | | |
| D2 | | | | |
| D3 | | | | |
| D4 | | | | |
| D5 | | | | |

b) Signs of hypocalcemia : +/-

| Day | Chvosteks - sluggish/brisk | Trousseaus-Time to positive |
|---|---|---|
| D1 | | |
| D2 | | |
| D3 | | |
| D4 | | |
| D5 | | |

c) Investigations:

| Investigation | D1 | D2 | D3 | D4 | D5 | D6 | D7 |
|---|---|---|---|---|---|---|---|
| 1. Ca | | | | | | | |
| 2. Alb | | | | | | | |
| 3. Mg | | | | | | | |
| 4. P | | | | | | | |
| 5. PTH | | | | | | | |

Patients who have received correction for hypomagnesemia – PTH repeated after correction

d) Calcium requirement post op:

Oral dose:

| | Calcium supplement | Dose |
|---|---|---|
| D1 | | |
| D2 | | |
| D3 | | |
| D4 | | |
| D5 | | |
| D6 | | |
| D7 | | |

IV requirement:

e) Vitamin D requirement postoperative:

Oral dose:

| | |
|---|---|
| Dose | |

f) Mg requirement Postop:

Oral/IV (dose) -

| | |
|---|---|
| Dose | |

**15. HPE report**:

**16. Re-exploration**: Yes/No

## Patient recruitment

Patients were recruited from the Endocrine Surgery OPD after obtaining a signed informed consent. In the OPD, patient details including demographic data, indication for surgery and the proposed operative procedure were entered. Chvostek's sign was elicited by tapping the cheek in the region of the anterior border of the masseter (Chvostek type II). Contraction of the facial muscles indicated a positive test. The result was entered as 'absent', 'sluggish' or 'brisk'**.** Preoperative blood samples were collected from the OPD/ward as shown in the table below.

**Table 1: Preoperative investigations performed and their reference range**

| S. No. | Preoperative Investigations | Normal Values |
|---|---|---|
| 1 | S. Calcium | 8.3 - 10.4 mg/dl |
| 2 | S. Albumin | 3.5 – 5 g/dl |
| 3 | S. Magnesium | 1.8 – 2.4 mg/dl |
| 4 | S. Phosphorous | 2.5 – 4.6 mg/dl |
| 5 | S. PTH | 8– 74 pg/ml |
| 6 | Vitamin D | >20 ng/ml |
| 7 | S. Alkaline Phosphatase | 40 – 125 U/L |

## Definitions

The definitions used in this study were based on biochemical values irrespective of presence or absence of clinical symptoms and signs, as defined below.

1) Hypocalcemia: corrected calcium of < 8.0 mg/dl.

{Corrected calcium was calculated using the formula: Corrected calcium = S. Calcium + 0.8 (4 – S. Albumin)}

2) Hypomagnesemia: S. magnesium < 1.8mg/dl.
3) Hypophosphatemia: S. phosphorous < 2.5mg/dl.
4) Hypovitaminosis: Vitamin D $\leq$ 20ng/ml.
5) Hypoparathyroidism: PTH < 8pg/ml.

## Laboratory methods used

The laboratory methods used for the various investigations performed are listed below.

A) Photometric method using the modular P800 automated analyser (Roche) to estimate:

1) S. Calcium

2) S. Magnesium

3) S. Phosphorous

4) S. Albumin

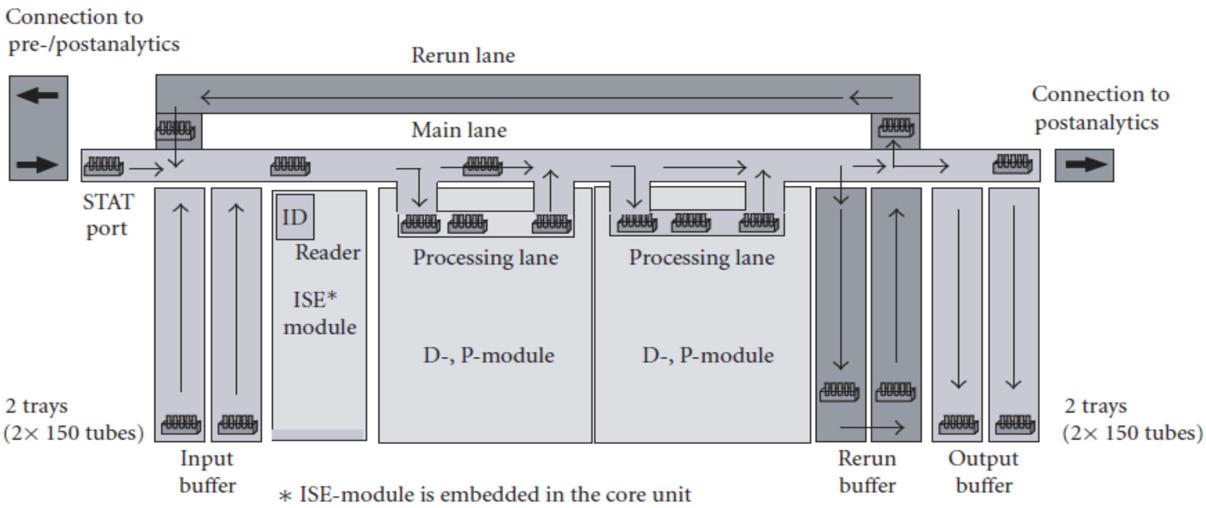
5) S. Alkaline Phosphatase

Principle of the method:

The sample and the reagent are mixed and this results in a coloured compound. A beam of light is transmitted through the coloured solution. This beam loses intensity as part of the light is absorbed. This absorption occurs at a particular wavelength. Result is interpreted by the system.

**Figure 4a: Photometric analyser (MODULAR P800)**

**Figure 4b: Schematic structure of MODULAR P 800** (78)




B) Serum iPTH (intact parathormone) was estimated by chemiluminescence using the Adiva centaur centre (Siemens)

Method: Patient sample centrifuged at ≥ 1000 x g for 15-20min

↓

200µL of sample dispensed in curette

↓

50µL of Lite reagent dispensed and incubate for 5 minutes at 37°C

[Lite reagent: contains two antihuman PTH antibodies

- A polyclonal goat antihuman PTH (N terminal 1-34) antibody labelled with acridinium ester
- Biotinylated polyclonal goat antihuman PTH (39-84 region) antibody]

↓

200µL of solid phase dispensed and incubate for 2.5 min at 37°C

(Streptavidin in solid phase is covalently coupled to paramagnetic latex particle)

↓

Separate, aspirate, wash curette with reagent water

↓

300µL each of acid and base reagent dispensed to initiate chemiluminescent reaction

↓

Result reported

**Figure 5: PTH analyser**

C) Serum vitamin D was estimated by electrochemiluminescence (Roche)

Method:

i. 1st incubation

15μL sample incubated with pretreatment reagent. Bound 25(OH) vitamin D released from vitamin D binding protein

ii. 2nd incubation

Pretreated sample incubated with ruthenium labelled vitamin D binding protein.

A complex between 25(OH) vitamin d and ruthenylated vitamin D binding protein formed

iii. 3rd incubation

Addition of streptavidin coated microparticles and 25(OH) vitamin D labelled biotin.

Free sites of ruthenium labelled vitamin D binding protein becomes occupied, forming a complex consisting of ruthenium labelled vitamin D binding protein and biotinylated 25(OH) vitamin D

↓

Entire complex bound to solid phase via interaction of biotin and streptavidin

↓

Reaction mixture aspirated into measuring cell

↓

Microparticles magnetically captured onto cell surface of electrode

↓

Unbound substance removed

↓

Application of voltage to electrodes induces chemiluminescent emission

↓

Measured by photomultiplier

## Intraoperative recording

The duration of the procedure (in minutes), parathyroid status (number seen, number preserved and the number auto-transplanted), and the volume of intravenous fluids used (in millilitres) were documented.

## Postoperative assessment

Signs (Chvostek, Trousseau’s) and symptoms of hypocalcemia were documented on all days of admission and on the first review in the OPD. The hypocalcemic symptoms if present were graded as occasional tingling of fingers/toes, severe paresthesia, mild cramping of the hand or severe cramping. Trousseau’s sign was evaluated by inflating the sphygmomanometer cuff to 20mmHg above the systolic blood pressure for one minute. Presence of carpal spasm indicated a positive test. The result was documented as being positive or negative. In patients with a positive Trousseau's sign, the time to positivity was also recorded in seconds.

Blood samples were collected in the postoperative period as depicted in table 2. On first post-operative day (day following the operation) all the investigations were sent. On day two onwards only serum calcium, magnesium and phosphorous were evaluated.

Patients who had undergone a hemithyroidectomy were discharged the next day and reviewed in OPD after 3-5 days. All patients following total thyroidectomy +/- modified radical neck dissection (MRND) were monitored for hypocalcemia for two days. Patients with normal serum calcium and asymptomatic for hypocalcemia were discharged on postoperative day two. All patients were initially prescribed calcium carbonate (Sandocal) 1gm at bedtime.

## Postoperative hypocalcemia

The patients in whom there was a fall in calcium on postoperative day two (<8.0mg/dl) with signs/symptoms of hypocalcemia, and the patients who had severe hypocalcemic symptoms with low normal S. calcium were not discharged on day two. In these patients the dosage of oral calcium was gradually increased [up to a maximum of 4gm daily] and calcitriol (Rocaltrol) was added starting at 0.25mcg once daily, increasing the dosage till the patient was asymptomatic [up to a maximum of 0.5mcg thrice daily]. Those patient's, who persisted to have symptomatic hypocalcemia in spite of being on maximum supplements, were given intravenous calcium gluconate infusion over twenty four hours. Additionally if they were found to be hypomagnesemic, intravenous infusion of magnesium sulphate, 10mg, thrice daily for three days was administered. Serum PTH was rechecked after completion of infusion in these patients.

**Table 2: Investigations performed in the postoperative period***

| Postop day | S. Calcium | S. Albumin | S. Magnesium | S. Phosphatase | S. PTH |
|---|---|---|---|---|---|
| 1 | + | + | + | + | + |
| 2 | + | | + | + | |
| 4 | + | | + | + | |
| 6 | + | | + | + | |

(*If patients were still admitted in the ward after postoperative day 2 for hypocalcemia, S. calcium, phosphorous and magnesium was checked on all days till discharge, and then at first review in the OPD.)

The dosage of oral calcium carbonate and calcitriol administered for each patient was recorded. Intravenous calcium gluconate and magnesium sulphate requirements were also recorded. The final histopathology and weight of the gland were noted. Due to the lack of substantial evidence for the role of calcitonin leak causing hypocalcemia we did not evaluate this risk factor in our study.

## Inclusion criteria

All adult patients undergoing thyroidectomy for benign or malignant disorders of the thyroid were included in the study.

## Exclusion criteria

The following patients were excluded from the study,

a) Patients who chose not to participate in the study.

b) Patients with an associated parathyroid disorder.

c) Patients in whom none of the pertinent biochemical parameters have been assessed.

## Statistical analysis

The statistical analysis was performed using STATA I/C 10.1. The descriptive statistics were performed using mean with standard deviation or frequency with percentages. Preoperative tests were assessed for correlation using the correlation coefficient. Chi square and independent T test were used to assess the association between postoperative hypocalcemia and hypomagnesemia as well as the association between hypocalcemia and other clinical variables. A significant association was defined with a p value of less than 0.05. The trends were represented with a line graph. The accuracy of PTH as a diagnostic test was evaluated using the ROC curve.

This study was approved by the institution review board (IRB minute number 7882). This study has also been registered in the clinical trials registry of India (CTRI), registration number is CTRI/2013/12/004195.

# Results

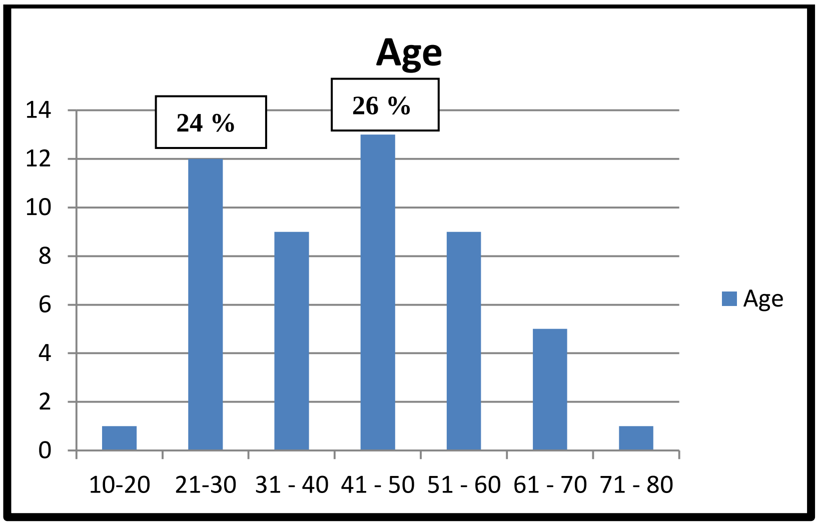
## A) Demographic profile

### 1) Age

The decade wise distribution of the population in this study group is depicted in the figure below. The youngest patient was eighteen years old and the oldest seventy five. The mean age was 42.5.

The peak age of presentation was in the fifth decade followed closely by the third decade.

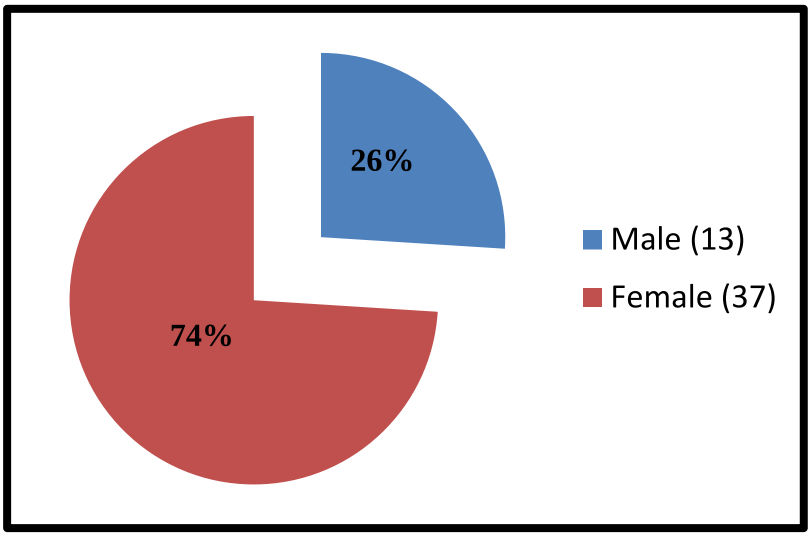
**Figure 6: The distribution of age of the patients**




### 2) Gender

Thyroid disorders are known to affect women more than men. As was expected there was a predominance of female patients (74%) who underwent thyroidectomy.

**Figure 7: Distribution of gender (No.)**




3) **Indication for operation and final diagnosis**

Majority of our patients (62%) were operated for either a suspicion of malignancy (32%) or a proved malignant lesion (30%). The remaining 38% of patients were operated upon for a probable benign goitre. The most common indication for operation among the benign goitres was pressure symptoms (42%). Four patients (21%) were thyrotoxic, among them three had Graves' disease and one a toxic nodule. The indication for operation among the benign goitres is shown in table 3.

**Figure 8: Indication for operation (no.)**

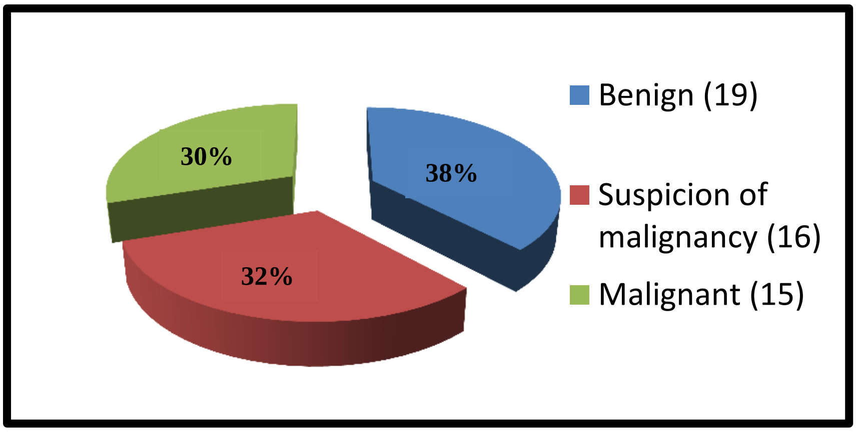


**Table 3: The indication for operation among the benign goiters**

| Benign (19) – Indication for operation | No. (%) |
|---|---|
| 1.Pressure symptoms | 8 (42%) |
| 2. Toxic goitre | 4 (21%) |
| 3. Patient's wish | 4 (21%) |
| 4. Recurrent goitre | 2 (11%) |
| 5. Retrosternal goitre | 1 (5%) |

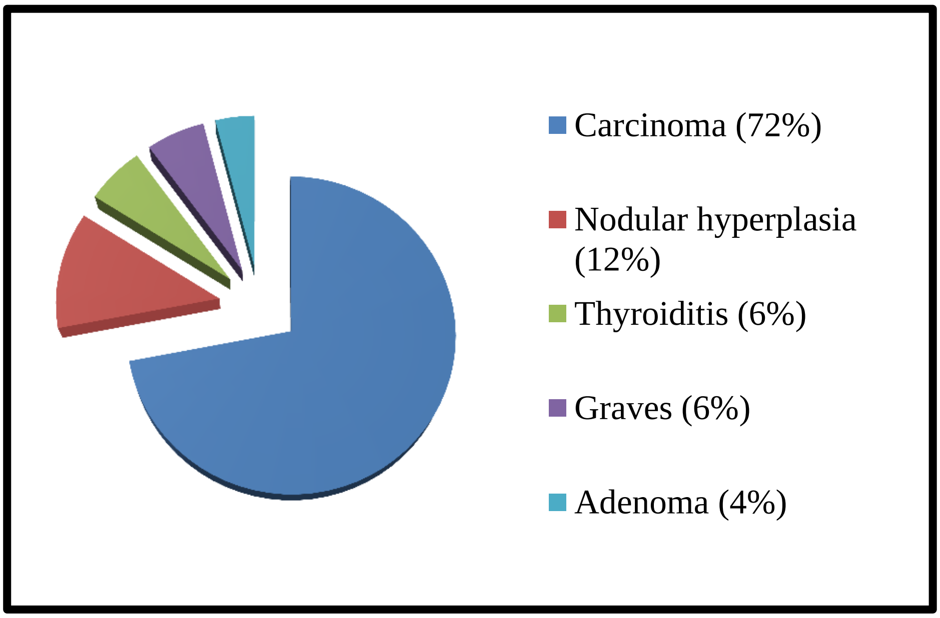
In the final diagnosis seventy four percent were malignant. Being a tertiary care referral center we see a high proportion of cancer in the referred cases. Among the malignancies, papillary carcinoma thyroid was the most common accounting for ninety four percent.

The majority of the patients that presented to us in the fifth decade had a malignant thyroid (69.2%). In the second peak that was witnessed (third decade) eleven out of the twelve patients (91.6%) had a malignant thyroid.

Our data showed that twenty five out of the thirty seven females (67.5%) and eleven out of the thirteen males (84.6%) had a malignant thyroid. Therefore the malignancy rate was higher in male patients with goitre.

Details of the final histopathology are shown in the figure below.

**Figure 9: Distribution of the final histopathology (%)**



4) **Preoperative Chvostek sign**

It was interesting to note that eight patients, 16% had a positive Chvostek's preoperatively. None of these patients had a preoperative low calcium or magnesium.

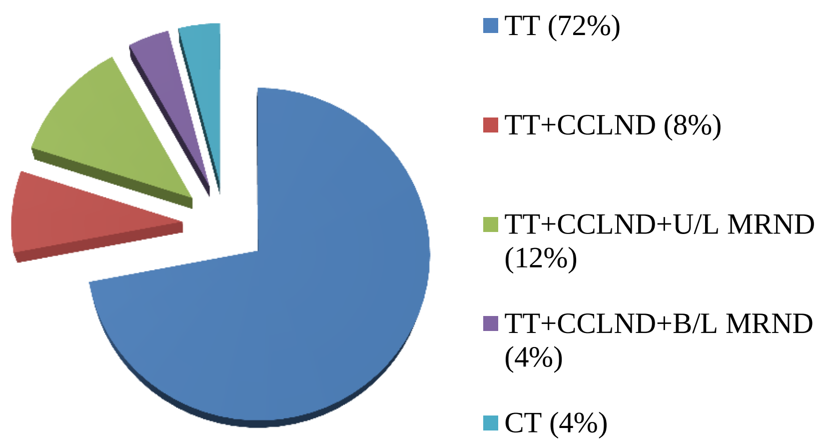
**Table 4: Preoperative Chvostek sign**

| **Positive** | **Negative** |
|---|---|
| 8 (16%) | 42 84%) |

5) **Operation performed**

Total thyroidectomy was the most common operation performed (72%). The other types of operations performed are depicted below.

**Figure 10: The types of operation performed with percentages**

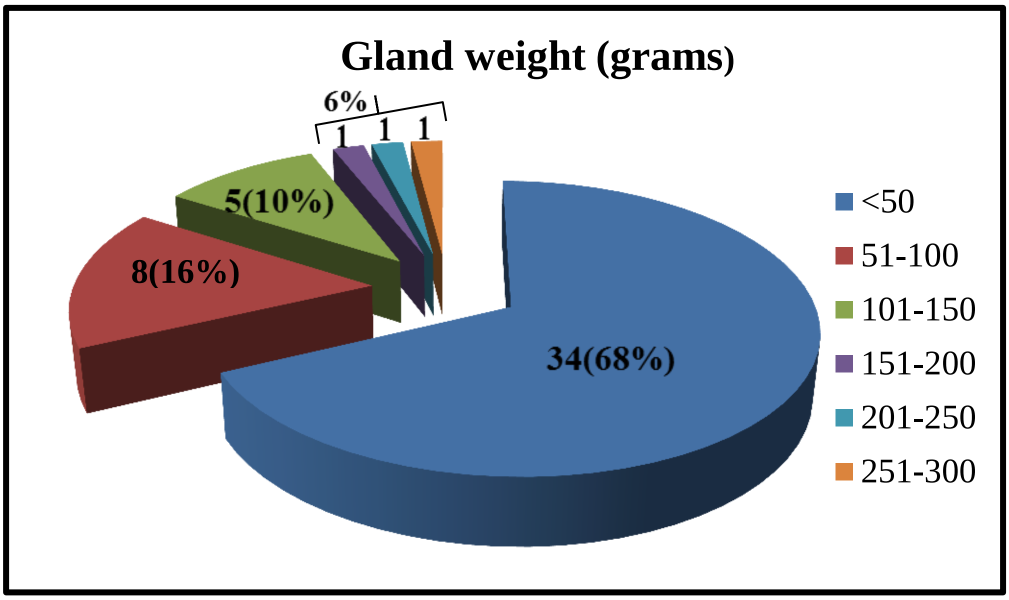



TT – total thyroidectomy, CCLND – central compartment neck dissection, MRND – modified radical neck dissection, CT – completion thyroidectomy

### 6) Gland weight

The weight of the largest gland was 300gm and the smallest 8gm. This was a completion thyroidectomy specimen. The weight of the smallest total thyroidectomy specimen was 10gm. The mean weight was 58.9. Considering that the normal thyroid gland weighs 20gm, the majority (68%) of the thyroid glands operated upon were small, weighing 50g or less. The correlation of weight of gland and hypocalcemia in literature was performed using 100g as the cutoff weight hence we looked for an association between these two factors keeping the same cutoff. There were forty two patients with gland weighing 100g or less and eight with weight above 100g. We found no significant association (p= 0.18).

**Figure 11: Distribution of gland weight**




### B) Preoperative investigations

**a) Calcium** – There were four patients with corrected calcium values between 8 to 8.29mg/dl. The value for one patient was 7.8mg/dl. The remaining forty five patients corrected calcium was within our laboratory reference range.

**Table5a: Distribution of preoperative calcium values**

| Calcium < 8.3mg/dl | Calcium 8.3 – 10.4mg/dl |
|---|---|
| 5 (10%) | 45 (90%) |

**Table 5b: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative calcium**

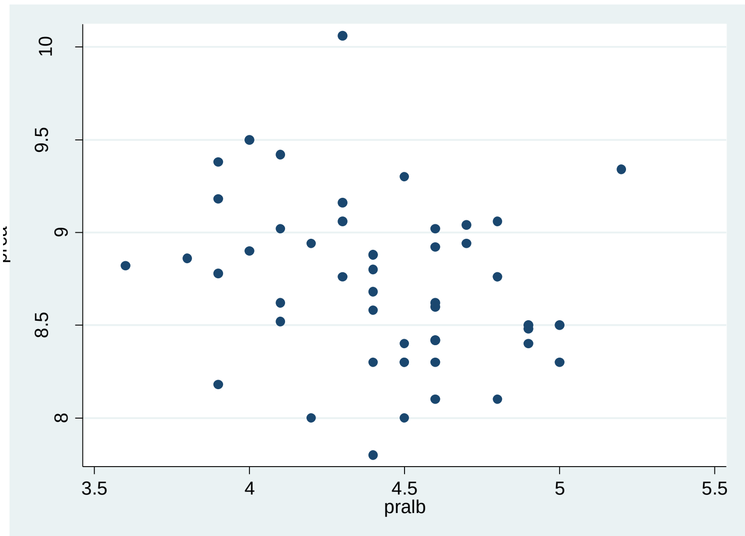
| Total No. | Mean | S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| 50 | 8.72 | 0.44 | 7.8 | 8.76 | 10.06 |

b) **Albumin** - All patients had values within the laboratory range preoperatively.

**Table 6: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative albumin**

| Total No. | Mean | S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| 50 | 4.43 | 0.35 | 3.6 | 4.45 | 5.2 |

**Figure 12: Depicting the correlation between preoperative calcium and albumin values**




Correlation coefficient = - 0.23

c) **Magnesium** – Twelve patients (24%) had hypomagnesemia prior to operation. Hence the prevalence of hypomagnesemia in the subset of patients undergoing thyroidectomy is 24%.

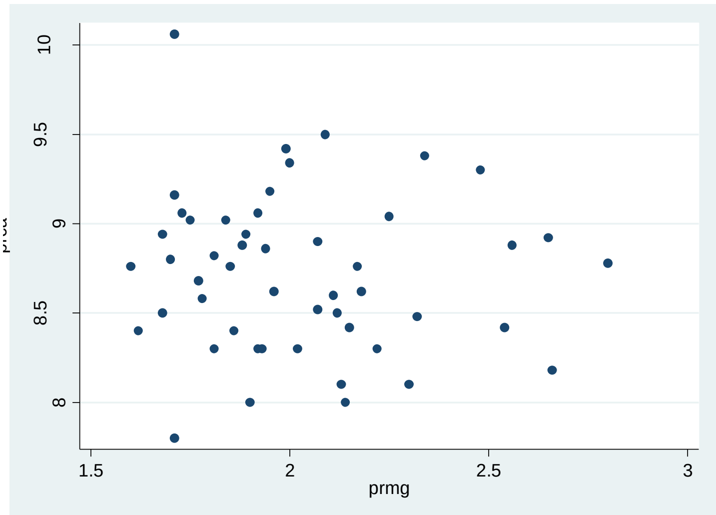
**Table 7a: Distribution of pre-operative serum magnesium values**

| Magnesium (mg/dl) | Freq. | Percent (%) |
|---|---|---|
| 1.6 – 1.79 | 12 | 24 |
| 1.8 – 2.4 | 32 | 64 |
| >2.4 | 6 | 12 |

**Table 7b: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative magnesium**

| Total No. | Mean | S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| **50** | **2.03** | **0.29** | **1.6** | **1.96** | **2.8** |

**Figure 13: Scatter plot depicting the correlation between preoperative calcium and magnesium values**



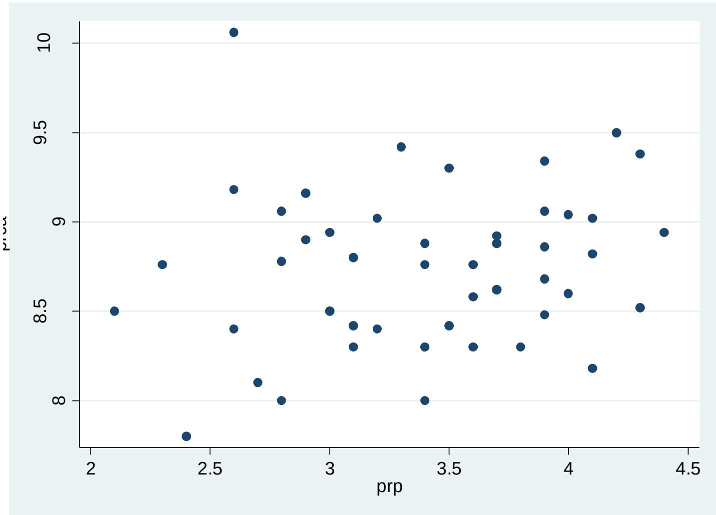

Correlation coefficient = - 0.07

**d) Phosphorous** – Only three patients had a phosphorous value below the laboratory reference range preoperatively. The phosphorous values for these three patients were 2.1, 2.3 and 2.4mg/dl.

**Table 8: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative phosphorous**

| Total No. | Mean | S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| **50** | **3.39** | **0.58** | **2.1** | **3.4** | **4.4** |

**Figure 14: Scatter plot depicting the correlation between preoperative calcium and phosphorus values**




Correlation coefficient = 0.19

e) **Vitamin D** – Thirty one patients (62%) were vitamin D deficient prior to operation.

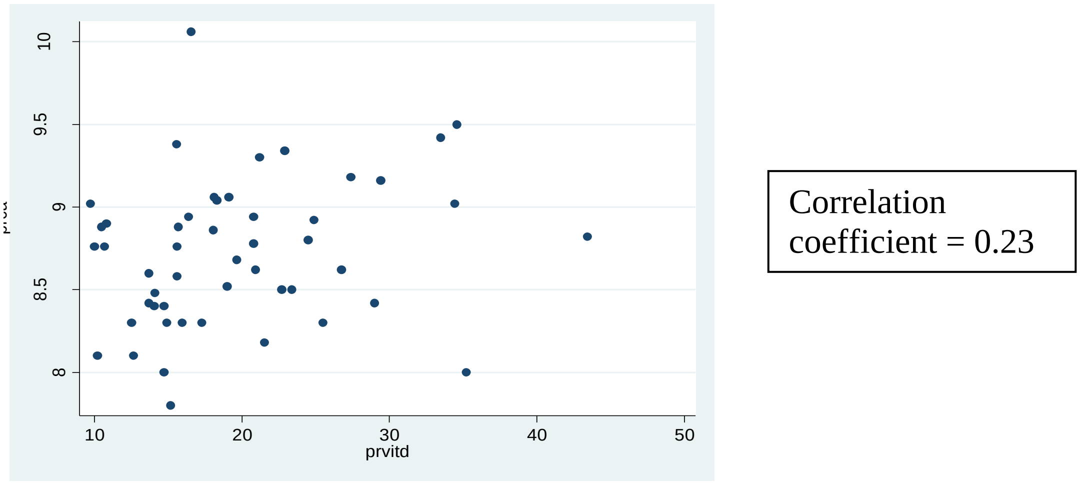
**Table 9a: Distribution of vitamin D**

| Vitamin D(ng/ml) | Freq. | Percent (%) |
|---|---|---|
| $\leq 20$ | 31 | 62 |
| $> 20$ | 19 | 38 |

**Table 9b: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative vitamin D**

| Total No. | Mean | S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| 50 | 19.72 | 7.59 | 9.74 | 18.1 | 43.45 |

**Figure 15: Scatter plot depicting the correlation between preoperative calcium and vitamin D values**




**i)Vitamin D and preoperative calcium**

Among the 31 patients with low vitamin D, five patients (16%) had calcium values below the laboratory reference range (<8.3mg/dl). Only one patient had hypocalcemia. The calcium of this patient was 7.8mg/dl. None of the patients with normal vitamin D had hypocalcemia.

**ii) Vitamin D and preoperative magnesium**

Nine out of thirty one patients (29%) with low vitamin D had hypomagnesemia. Of the remaining nineteen patients in whom the vitamin D values were normal, three patients had hypomagnesemia.

**iii) Vitamin D and PTH**

Two out of thirty one patients (6.5%) with a low vitamin D had PTH less than 8. All other patients PTH were normal.

**iv) Vitamin D and Alkaline phosphatase**

Only five out of thirty one patients (16%) with hypovitaminosis D had an elevated alkaline phosphatase level. Two patients with normal vitamin D also had an elevated alkaline phosphatase value.

f) **PTH –** Thirty three patients (66%) had PTH value within the reference range. Seventeen patients (34%) the PTH values were out of the reference range. Since serum calcium and phosphorous were normal among these patients they were included in the study.

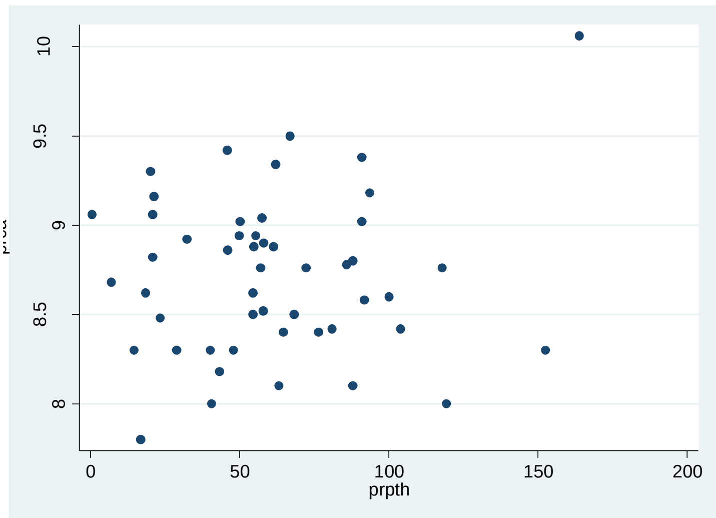
**Table 10a: Distribution of pre-operative PTH**

| **<8pg/ml** | **8 – 74pg/ml** | **>74pg/ml** |
|---|---|---|
| 2 (4%) | 33 (66%) | 15 (30%) |

**Table 10b: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative PTH**

| **Total No.** | **Mean** | **S.D.** | **Minimum** | **Median** | **Maximum** |
|---|---|---|---|---|---|
| **50** | **3.39** | **0.58** | **2.1** | **3.4** | **4.4** |

**Figure 16: Scatter plot depicting the correlation between preoperative calcium and PTH values**




Correlation coefficient = 0.11

g) **S. Alkaline phosphatase –** Seven patients (14%) had an elevated alkaline phosphatase value. One of these patients had a toxic nodule. The remaining six patients with elevated alkaline phosphatase values were euthyroid.

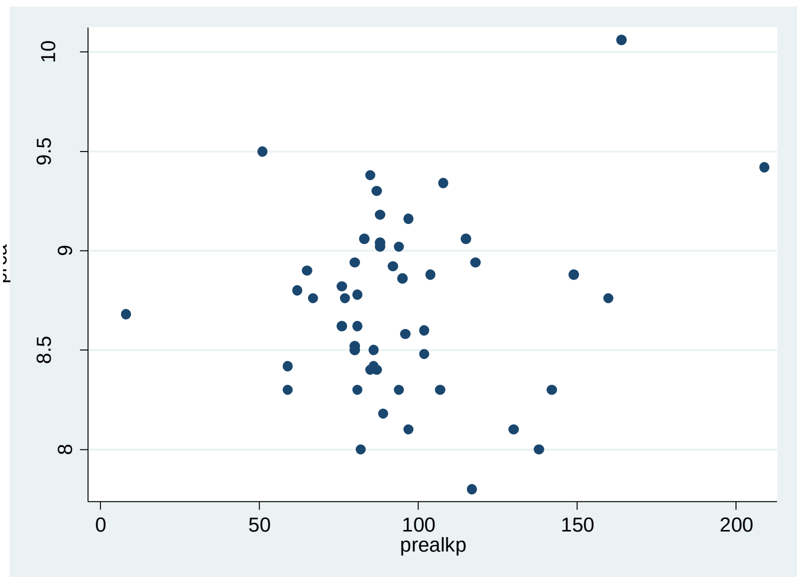
**Table 11a: Distribution of alkaline phosphatase**

| **<40U/L** | **40-125U/L** | **>125U/L** |
|---|---|---|
| **1 (2%)** | **42 (84%)** | **7 (14%)** |

**Table 11b: Depicting the mean, median, standard deviation (SD), Minimum and maximum values for preoperative alkaline phosphatase**

| **Total No.** | **Mean** | **S.D.** | **Minimum** | **Median** | **Maximum** |
|---|---|---|---|---|---|
| **50** | **94.94** | **32.02** | **8.1** | **88** | **209** |

**Figure 17: Scatter plot depicting the correlation between preoperative calcium and alkaline phosphatase values**




Correlation coefficient = 0.14

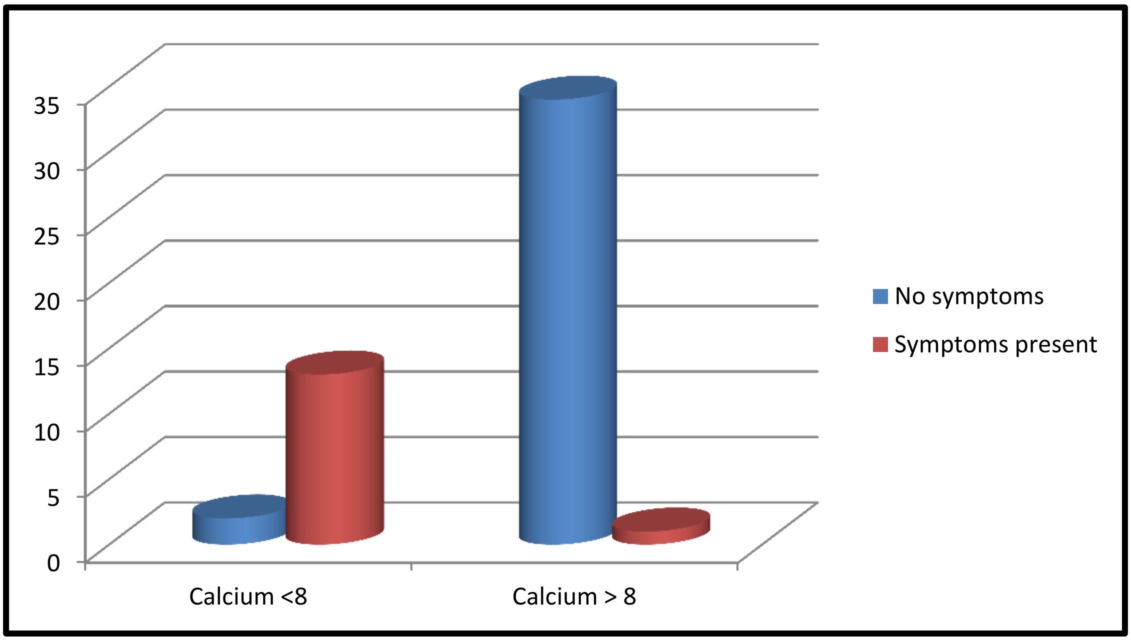
## C) Postoperative period

### 1) Symptoms of hypocalcemia

In the postoperative period thirteen patients had symptoms of hypocalcemia (26%). Among these thirteen patients, two patients had both Chvostek's and Trousseau's sign. These two patients had severe symptoms of hypocalcemia as well. Their serum calcium values were 7.4 and 7.6mg/dl. They both required intravenous calcium correction. The remaining eleven patients had no signs of hypocalcemia.

Twelve of these patients had biochemical hypocalcemia, which could be corrected with oral supplements of calcium alone. One patient though symptomatic for tingling had normal serum calcium. His preoperative calcium value was 9.1 and postoperatively 8.7 and 9.04mg/dl on day one and two respectively. Hence twelve out of the thirteen patients (92.3%) with symptoms of hypocalcemia in the postoperative period also had biochemical hypocalcemia, suggesting that symptoms of hypocalcemia are a good indication of the presence of hypocalcemia in the postoperative period.

**Figure 18: Depicting postoperative calcium level with symptoms of hypocalcemia**



**2) Signs of hypocalcemia**

a) **Chvostek's sign –** On the first postoperative day Chvostek's sign was positive in 16 patients. Eight of these patients (50%), had a preoperative positive sign. The grade of Chvostek's increased in the postoperative period in three patients while it remained the same in five.

b) **Trousseau's sign –** Only two patients had a positive Trousseau's sign. Both of these patients had severe symptoms of hypocalcemia requiring intravenous calcium correction. Both patients with positive Trousseau's sign were positive for Chvostek's sign as well.

Hence Trousseau's sign seems to be less sensitive but more specific for hypocalcemia than Chvostek's sign.

**3) Postoperative Investigations**

**a)** **S. Calcium –** On the first postoperative day, fifteen patients (30%) had biochemical hypocalcemia. This is our rate of hypocalcemia following thyroidectomy. We then observed that this reduced to eleven patients (22%) on day two and further to five patients (10%) by the day of outpatient review (day 5-8).

**Table 12: Depicting the postoperative calcium levels**

| **Day 1 Calcium** | **No. (%)** |
|---|---|
| **≥8** | **35 (70%)** |
| **< 8** | **15 (30%)** |

| **Day 2 Calcium** | **No. (%)** |
|---|---|
| **≥8** | **39 (78%)** |
| **< 8** | **11 (22%)** |

| **OPD review Calcium** | **No. (%)** |
|---|---|
| **≥8** | **45 (90%)** |
| **< 8** | **5 (10%)** |

b) **S. Magnesium –** Thirty five patients (70%) were hypomagnesemic on the first postoperative day. This decreased to thirty patients (60%) on second postoperative day and to nineteen patients (38%) by day of outpatient review (day 5-8).

**Table 13: Depicting the postoperative magnesium levels**

| POD 1 Magnesium | No. (%) |
|---|---|
| ≥ 1.8 | 15 (30%) |
| < 1.8 | 35 (70%) |

| POD 2 Magnesium | No. (%) |
|---|---|
| ≥ 1.8 | 20 (40%) |
| < 1.8 | 30 (60%) |

| OPD review Magnesium | No. (%) |
|---|---|
| ≥ 1.8 | 31 (62%) |
| < 1.8 | 19 (38%) |

c) **S. Phosphorous –** Evaluation of serum phosphorous revealed a gradual increase in number of patients with phosphorous above the normal value by the time they came for outpatient review.

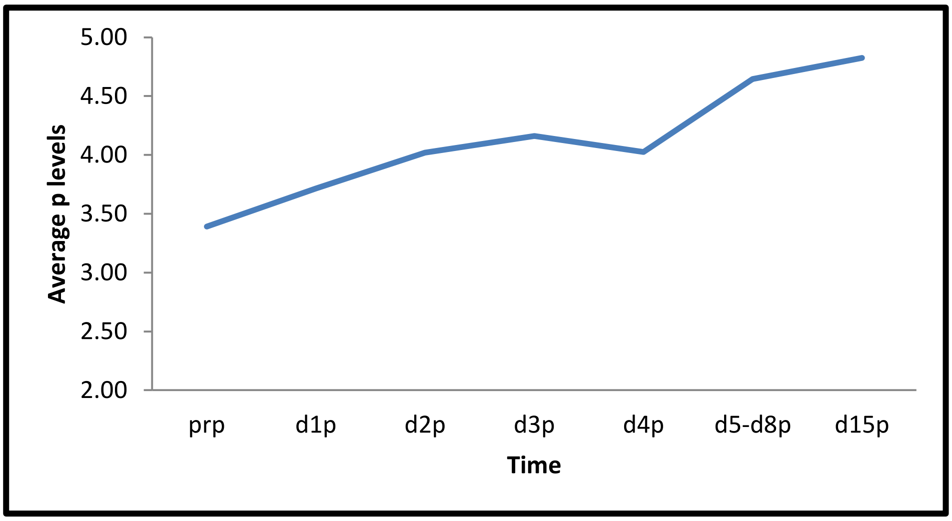
**Table 14: Depicting the postoperative phosphorous levels**

| POD 1 Phosphorous | No. (%) |
|---|---|
| < 2.5 | 6 (12%) |
| 2.5 – 4.6 | 36 (72%) |
| > 4.6 | 8 (16%) |

| POD 2 Phosphorous | No. (%) |
|---|---|
| < 2.5 | 1 (2%) |
| 2.5 – 4.6 | 40 (80%) |
| > 4.6 | 9 (18%) |

| OPD review Phosphorous | No. (%) |
|---|---|
| < 2.5 | 0 (0%) |
| 2.5 – 4.6 | 36 (72%) |
| > 4.6 | 14 (28%) |

**Figure 19: Depicting the trend of phosphorous in the postoperative period**



d) **PTH –** A large number of patients (40%) had postoperative day one PTH lower than the reference range, though only 28% had biochemical hypocalcemia on the same day.

**Table 15: Depicting postoperative PTH level**

| POD 1 PTH | No. (%) |
|---|---|
| < 8 | 20 (40%) |
| 8 – 74 | 28 (56%) |
| > 74 | 2 (4%) |

## D) Risk factors for post thyroidectomy hypocalcemia

### 1) Role of magnesium

Thirty five patients had hypomagnesemia in the postoperative period and not all these patients had hypocalcemia. Among the fourteen patients with hypocalcemia, only twelve had hypomagnesemia as well. We could not find a statistical significant association between postoperative hypocalcemia and hypomagnesemia (p=0.5).

Though no statistically significant association could be attained we could depict that both calcium and magnesium tend to fall below the normal range in the immediate postoperative period and both ions then start to normalize by end of the first week.

**Figure 20: Depicting the trends of calcium and magnesium in the postoperative period**

**Figure 20a: Preoperative calcium and magnesium values**

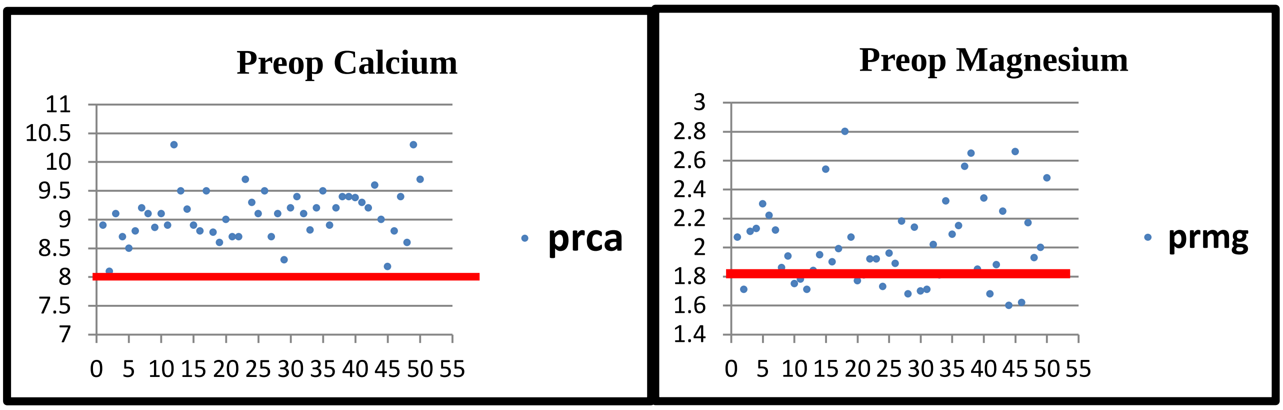
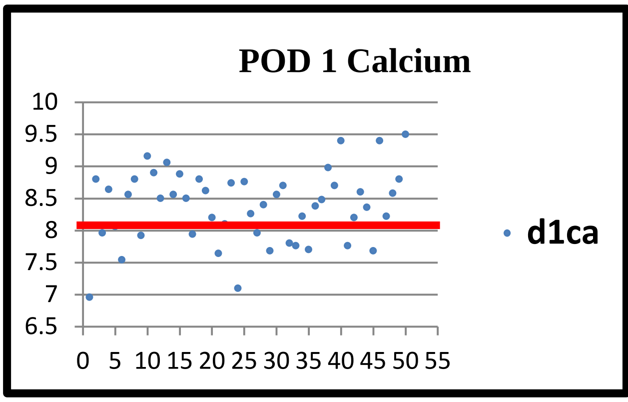


Figure 20b: Postoperative day 1 calcium and magnesium values



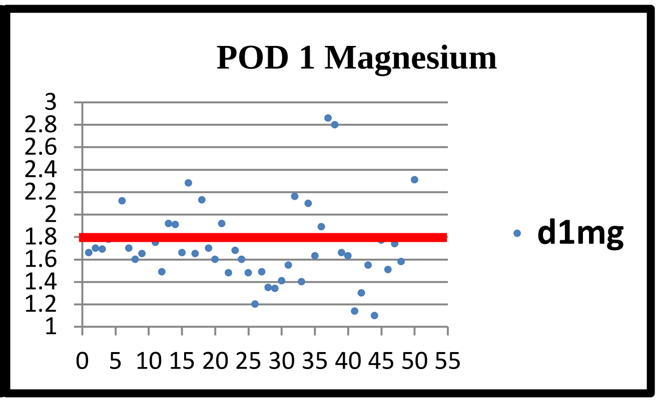
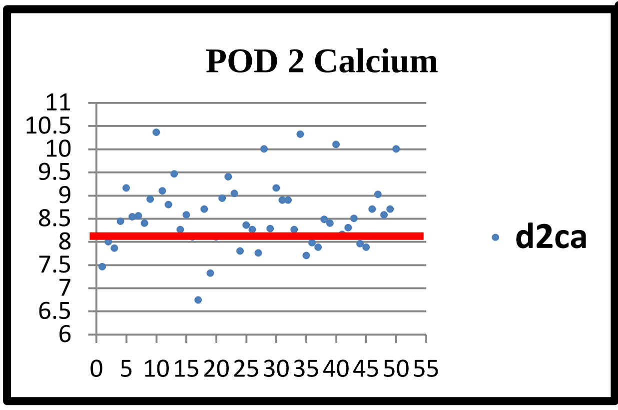




Figure 20c: Postoperative day 2 calcium and magnesium values



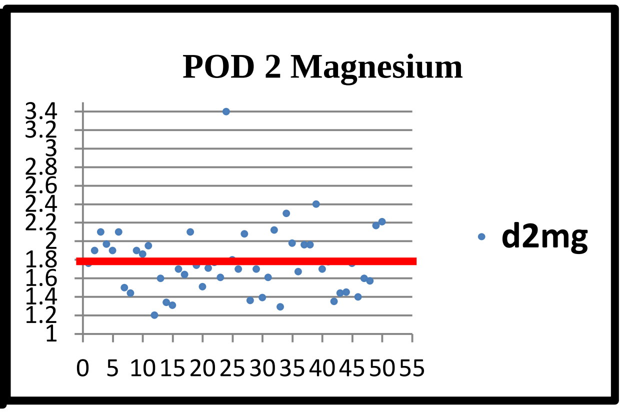
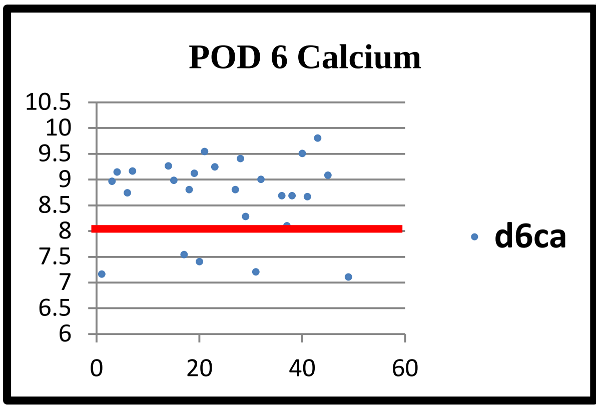




Figure 20d: Postoperative day 6 calcium and magnesium values



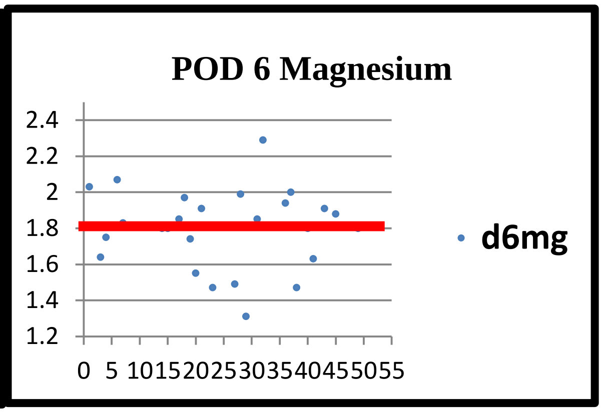



**Figure 20e: Graph depicting the trend of calcium in the postoperative period**

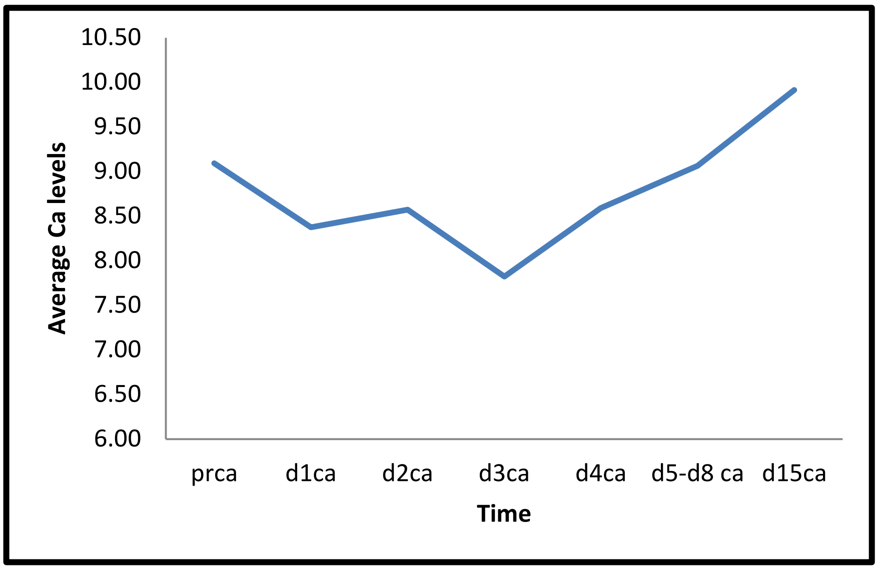
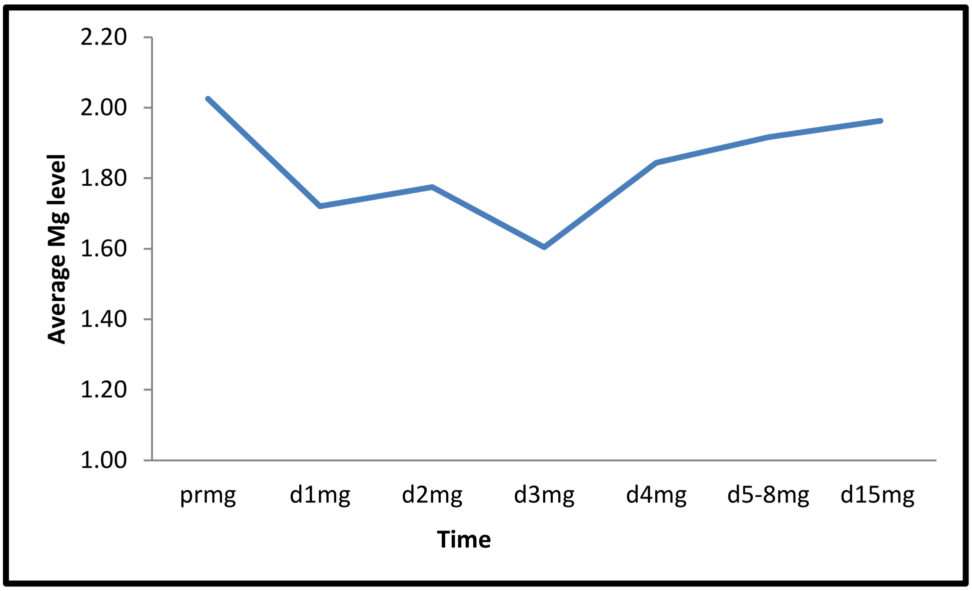


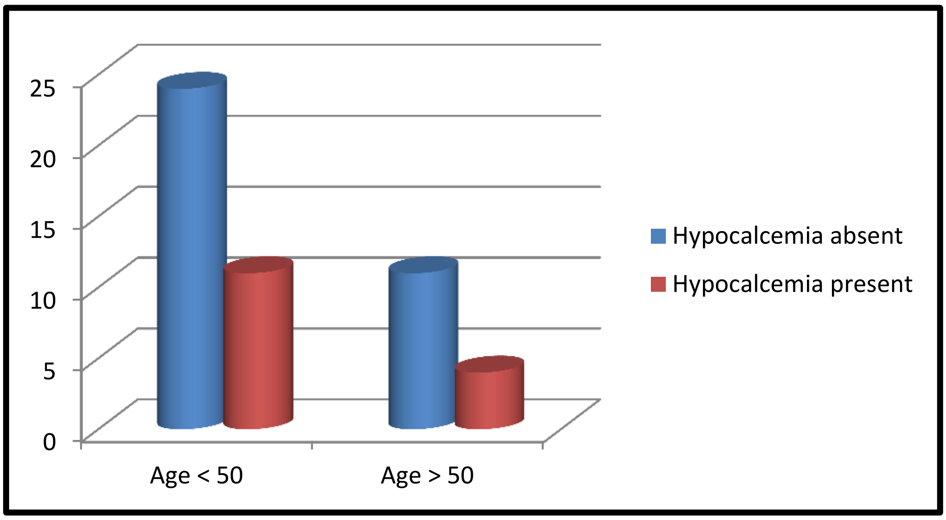

**Figure 20f: Graph depicting the trend of magnesium in the postoperative period**




### 2) Age

We assessed the risk of developing hypocalcemia postoperatively among patients aged above fifty years compared to those below fifty years. There were thirty five patients who were fifty years of age or less. Among these patients eleven developed hypocalcemia postoperatively (31.4%). Fifteen patients were above fifty years of age and among them four patients developed hypocalcemia (26.6%). There was no statistical association between age and risk of developing postoperative hypocalcemia (p= 0.409).

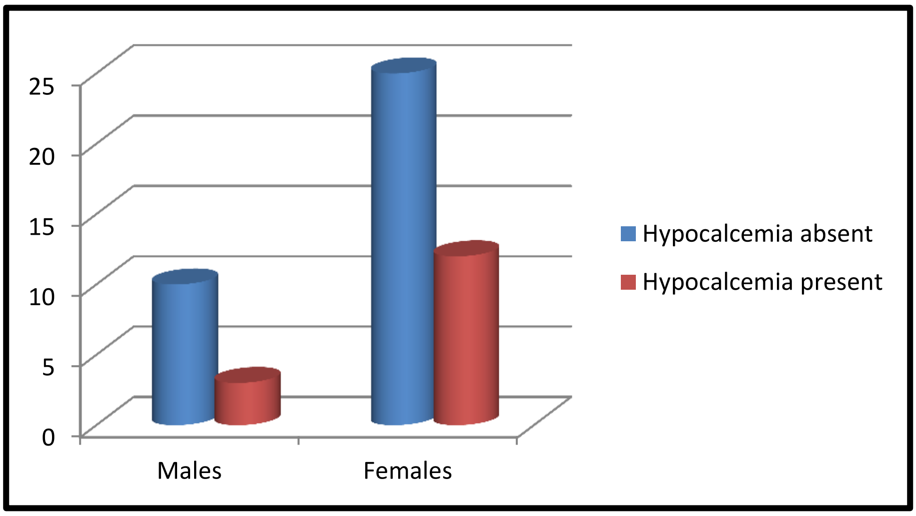
**Figure 21: Depicting age and postoperative hypocalcemia**




### 3) Gender

Twelve patients among the thirty seven females developed postoperative hypocalcemia (32.4%), whereas three out of the thirteen males developed hypocalcemia (23%). Gender was also found to have no association with the risk of developing postoperative hypocalcemia (p=0.646).

**Figure 22: Depicting gender and postoperative hypocalcemia**




### 4) Vitamin D

In our patients the majority with a preoperative low vitamin D had normal calcium levels postoperatively (50%). There was a significant association found between preoperative low vitamin D levels and normal calcemia (p= 0.0358) indicating that hypovitaminosis D may be protective against development of hypocalcemia.

**Table 16: Depicting vitamin D and hypocalcemia**

| Vitamin D value | POD 1 Calcium <8 mg/dl | POD 1 Calcium >8 mg/dl |
|---|---|---|
| Vitamin D ≤20 | 6 (12%) | 25 (50%) |
| Vitamin D >20 | 9 (18%) | 10 (20%) |

### 5) Thyrotoxicosis

Five patients had thyrotoxicosis prior to operation. Among these, three patients had Graves' disease while two had an autonomously functioning toxic nodule (AFTN). All patients were euthyroid prior to operation. In the postoperative period, persistent symptomatic hypocalcemia requiring IV magnesium was seen in one patient with toxic nodule. Interestingly alkaline phosphatase was elevated in this patient. Among the remaining four patients, two developed hypocalcemia. Both were patients with Graves' disease. All four patient's alkaline phosphatase was normal. Hence three of the five patients (60%) with thyrotoxicosis developed hypocalcemia postoperatively. The biochemical values for these five patients are shown in the table below.

**Table 17: Thyrotoxic patient's biochemical values**

| Diagnosis | Alk phos | Preop Ca | Preop Mg | Preop P | Postop Ca | Postop Mg | Postop P |
|---|---|---|---|---|---|---|---|
| **1.Graves'** | **85** | **9.3** | **2.34** | **4.3** | **8.6/9.3** | **1.6/1.7** | **3.4/4** |
| **2.Graves'** | **115** | **9.1** | **1.73** | **2.8** | **7.1/7.8/8.4** | **1.6/3.4/1.7** | **4.4/4.3** |
| **3.Graves'** | **76** | **8.5** | **1.81** | **4.1** | **7.7/8.2/8.6** | **1.4/1.3/1.5** | **3/4.8/5.1** |
| **4.AFTN** | **204** | **9.5** | **1.99** | **3.3** | **7.9/6.7/7.5/ 7.0/7.5/8.7** | **1.6/1.6/ 1.07/1.6/1.8** | **4.3/4.5/ 4.2/4.7/5** |
| **5. AFTN** | **118** | **9.5** | **1.89** | **4.4** | **8.2/8.2/9.3** | **1.2/1.7/1.8** | **4.7/4.5/4** |

Evaluating the presence of thyrotoxicosis as a risk of developing hypocalcemia we found no significant association (p=0.12).

We used alkaline phosphatase as a surrogate marker for bone health in patients with thyrotoxicosis. There were seven patients with elevated alkaline phosphatase level. Among these only one patient had thyrotoxicosis as explained above. Among the remaining patients with elevated alkaline phosphatase, four had a malignant thyroid, one patient an adenoma and the last patient had a nodular hyperplasia of the thyroid.

**Figure 23: Depicting the patients with normal and elevated alkaline phosphatase**

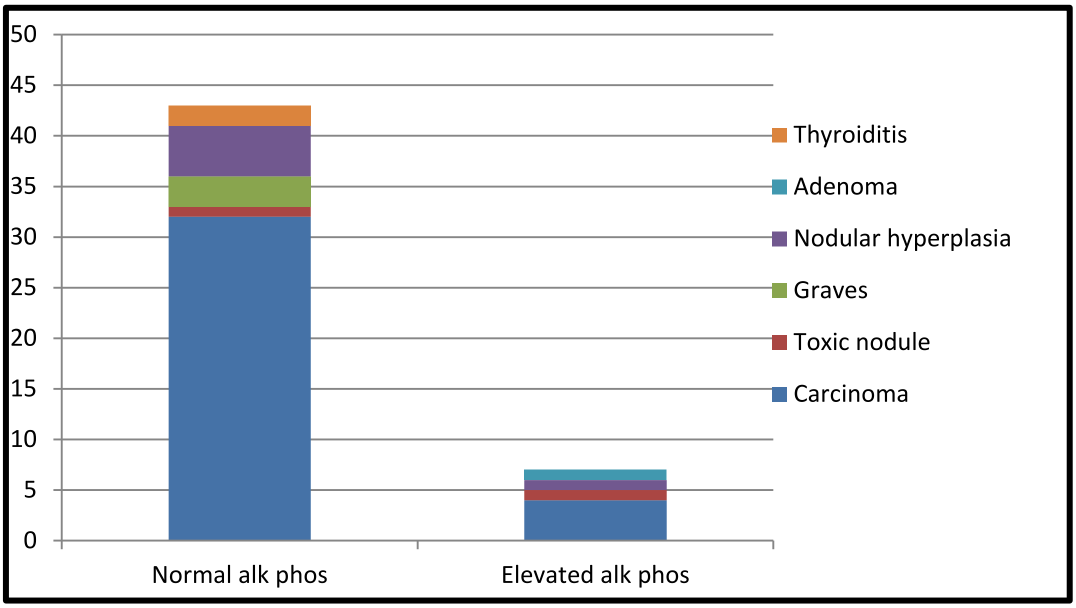
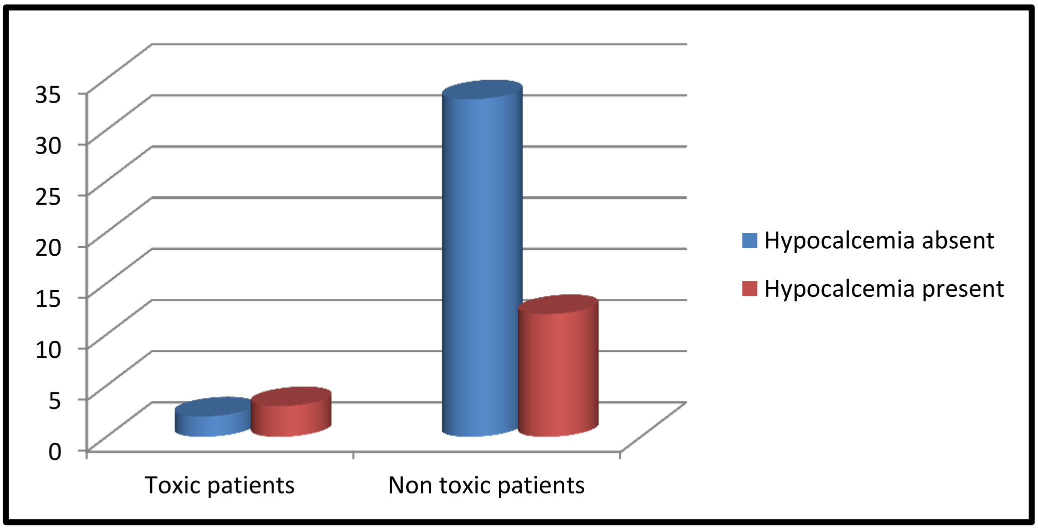


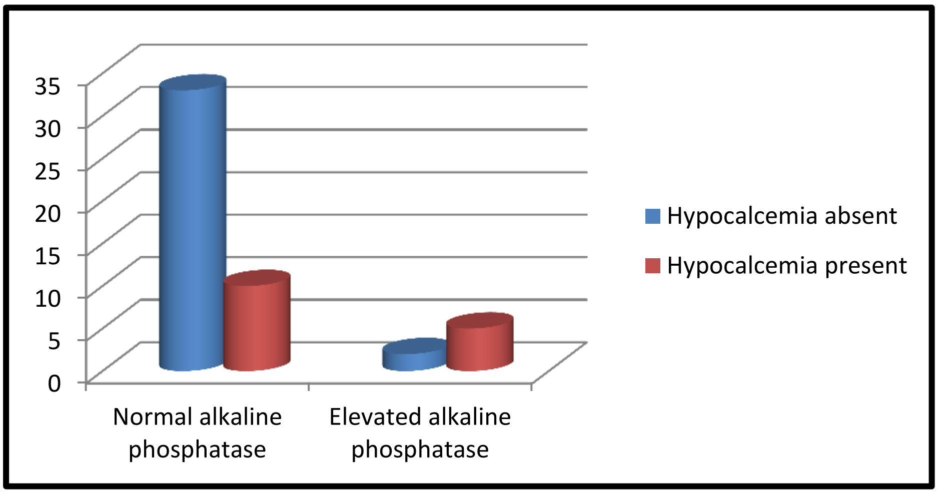

**Figure 24: Depicting the relationship between toxicity and hypocalcemia**



Five out of these seven patients developed postthyroidectomy hypocalcemia (71.4%). The patient with a toxic nodule was one among these.

In Forty three patients, the alkaline phosphatase was normal. Ten of these patients developed hypocalcemia (23.2%).

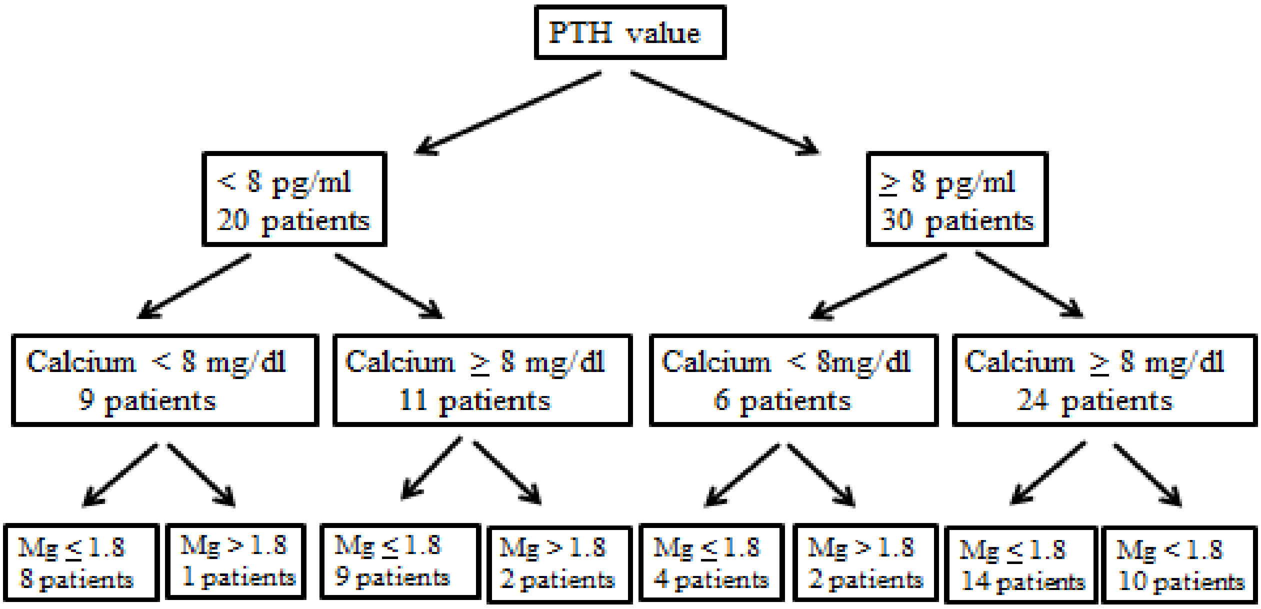
**Figure 25: Depicting the relationship between alkaline phosphatase and hypocalcemia**




**6) Parathyroid status**

Twenty patients had postoperative PTH below the normal reference range. Among these, nine patients (45%) had hypocalcemia. The PTH for these nine patients was very low (less than 3). The remaining eleven patients though PTH was low, they had normal calcium levels. PTH was less than 3 in six of these patients as well. We also observed that in six patients though the PTH was normal, they had hypocalcemia. Statistical analysis showed a significant association between PTH below the biochemical reference range (<8pg/ml) and the presence of postthyroidectomy hypocalcemia (p= 0.029).

**Figure 26: Depicting postoperative PTH, calcium and magnesium values**




Summarizing the relationship of hypomagnesemia with PTH and calcium from the above flow chart,

Low PTH + Low Ca + Low Mg = 8/9 patients (88.9%)

Low PTH + Normal Ca + Low Mg = 9/11 patients (81.8%)

Normal PTH + Low Ca + Low Mg = 4/6 patients (66.6%)

Normal PTH + Normal Ca + Low Mg = 14/24 patients (58.3%)

We observed that in the postoperative period as the calcium decreased the phosphorous increased. This further suggests the presence of hypoparathyroidism in the postoperative period. This relationship is depicted in the figure below.

**Figure 27: Depicting the calcium and phosphorous trend in the postoperative period**

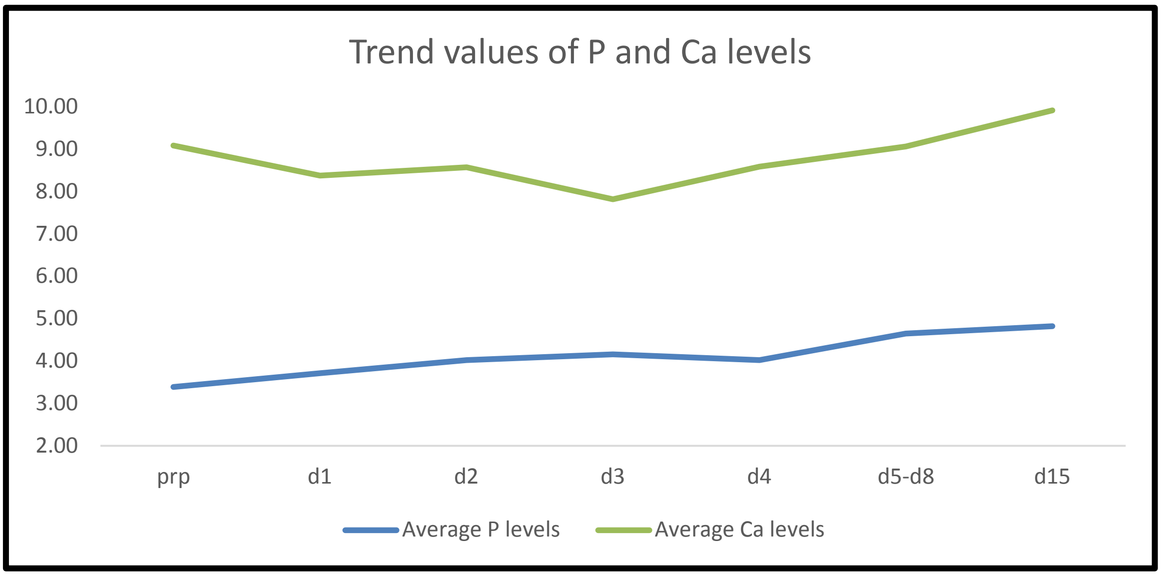
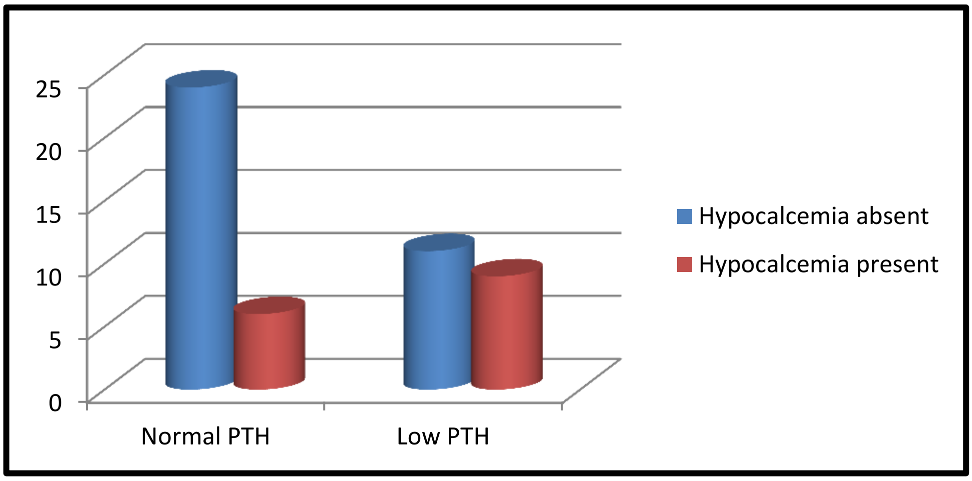


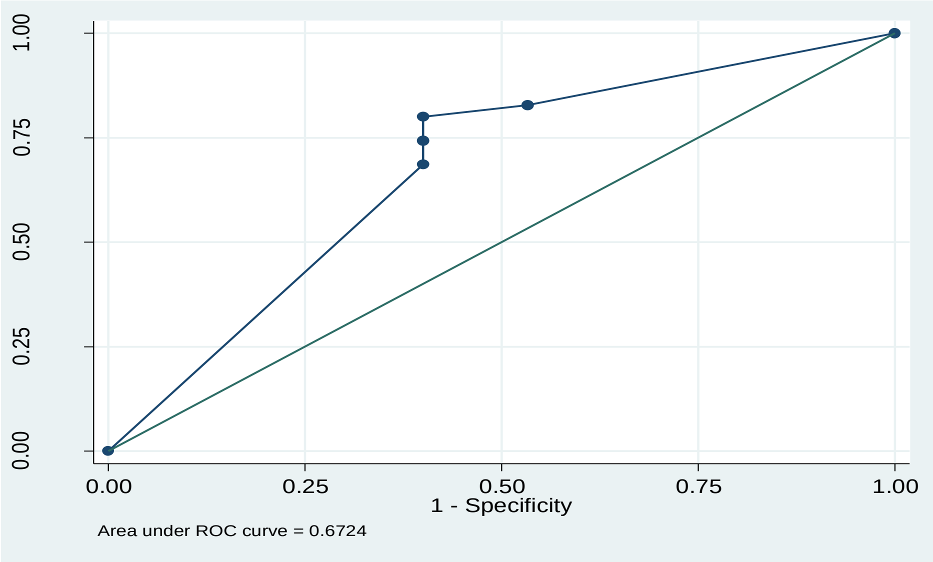

**Figure 28: Depicting PTH and hypocalcemia**




As all of the patients with hypocalcemia had a PTH less than 3 we assessed the risk of developing hypocalcemia in patients with PTH less than 3 and found a much stronger association (p= 0.004).

We further demonstrated this association by plotting the ROC curve and corresponding sensitivity and specificity as is seen below in the figure and table.

**Figure 29: The ROC curve**




Receiver Operating Characteristic (ROC) curve is a plot of the true positive rate against the false positive rate for the different possible cut-off points of a diagnostic test.

An ROC curve demonstrates (79):

1. The trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity).
2. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test.
3. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test.
4. The slope of the tangent line at a cut-off point gives the likelihood ratio (LR) for that value of the test.
5. The area under the curve is a measure of the tests accuracy.

The area under the curve for our study is 0.7 suggesting a good area under the curve. This indicates that PTH is an accurate test.

**Table 18: Sensitivity and specificity pattern**

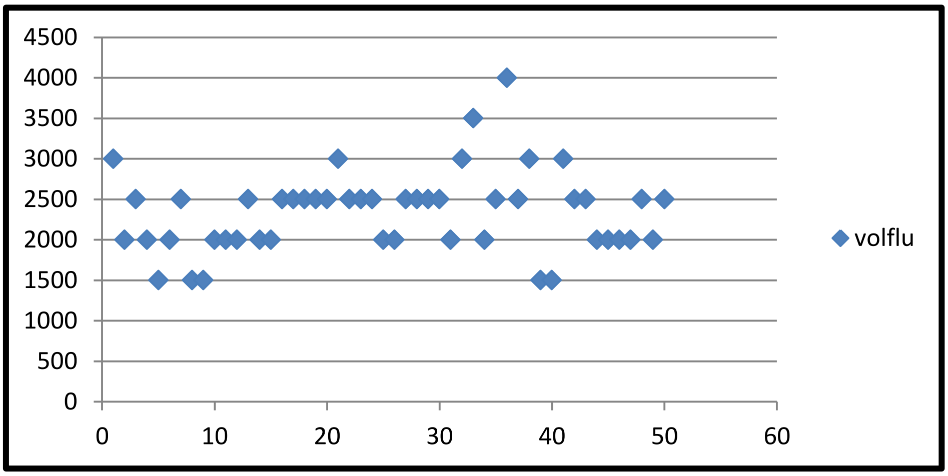
| PTH range | Sensitivity | Specificity |
|---|---|---|
| 0-2 | 100.00% | 0.00% |
| 2.1-4 | 82.86% | 46.67% |
| 4.1-6 | 80.00% | 60.00% |
| 6.1-8 | 74.29% | 60.00% |
| >8 | 68.57% | 60.00% |

From the table above we conclude that a PTH of 4.1- 6 may be used as a cutoff point since the sensitivity and specificity is the highest at this value.

### 7) Hemodilution

The volume of fluids used varied from 1500ml to a maximum of 4000ml. The average volume used was 2330ml. Majority of the patients (42%) received 2500ml of intravenous fluids in the perioperative period. A significant association between the volume of fluids used and the presence of postoperative hypocalcemia (p = 0.03) was observed. The greater the volume of fluids used peri/intraoperatively there was a greater risk of developing hypocalcemia postoperatively.

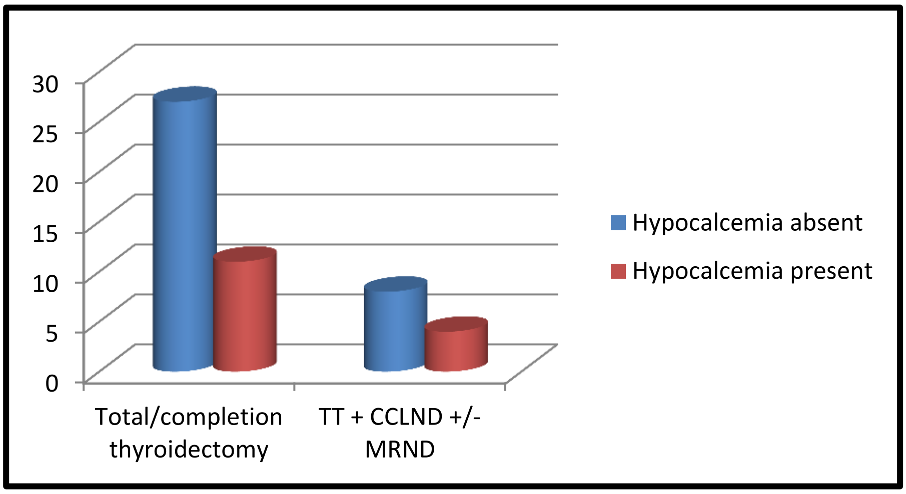
**Figure 30: Depicts the volume of fluid used perioperatively**




### 8) Extent of dissection

We compared patients who underwent total thyroidectomy or completion thyroidectomy alone to those who underwent a more extensive procedure with neck dissection. Majority of patients had undergone a total thyroidectomy/completion thyroidectomy (38 patients-76%). Eleven of these patients developed postoperative hypocalcemia (28.9%). Among the twelve patients who underwent more extensive surgery, four patients developed hypocalcemia (33.3%). There was no significant association between the extent of dissection and development of hypocalcemia in this study (p= 0.773).

**Figure 31: Extent of surgery and hypocalcemia**




### 9) Duration of surgery

Majority of the operations performed were within 120 minutes (68%). There were twenty two patients in whom the operation was completed in ninety minutes all of these were total thyroidectomies. We assessed the risk of developing hypocalcemia between operations completed within ninety minutes and those that took a longer time. The duration of the operation was not related with post thyroidectomy hypocalcemia (p=0.9).

**Figure 32: Duration of operation and hypocalcemia**

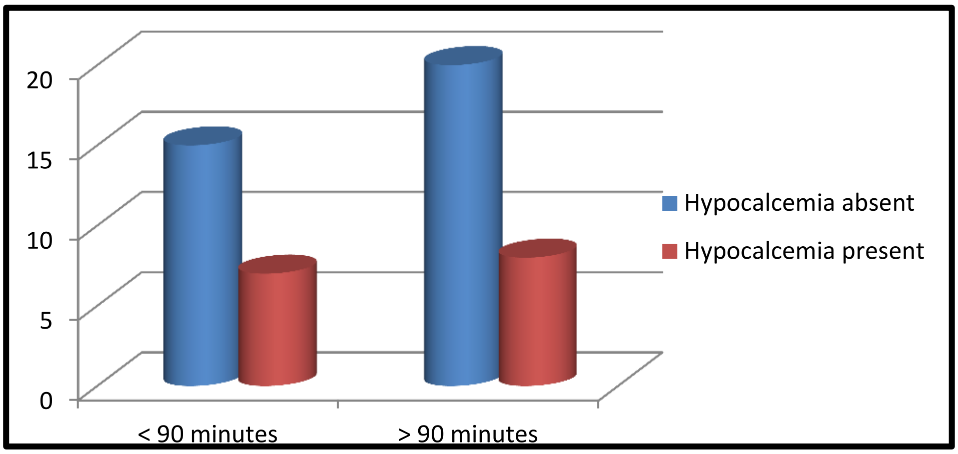
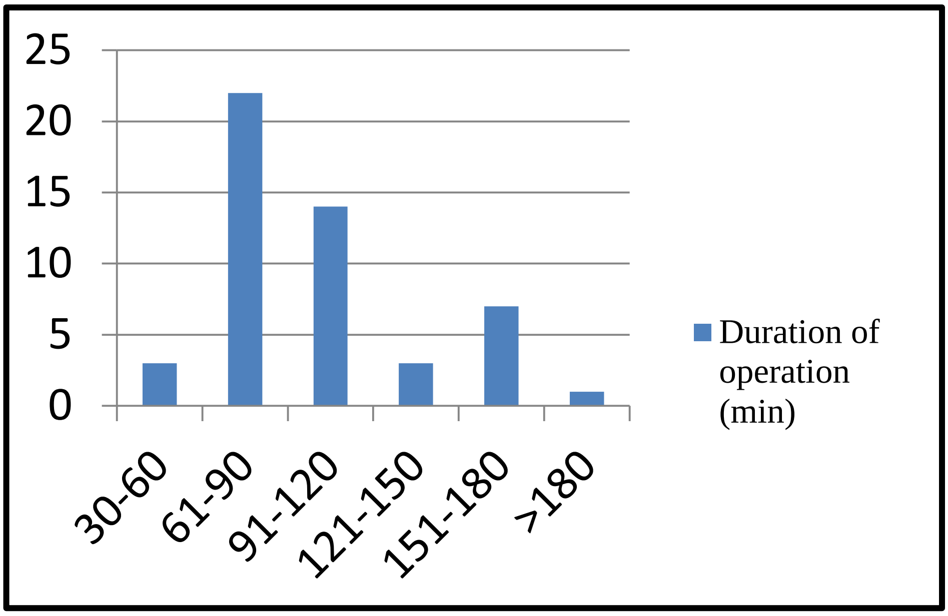



**Figure 33: Number of patients and duration of operation (min)**



# Discussion

Thyroidectomy is a common operation performed world over. As we know, one of the most feared complications following this procedure is permanent hypocalcemia. Persistent hypocalcemia is a phenomenon not well described. Our past experience with persistent hypocalcemia suggests a relationship with magnesium.

## A) Demographic profile

### 1) Age

The documentation of the age distribution of thyroid disorders in literature is stratified to either benign or malignant thyroid disease. Hence to compare the age distribution of all thyroid disorder together was difficult. Literature from South Africa and Zambia have shown similar mean age (46 and 42 years) of presentation as in our study, whereas 35.4 was the mean age in a report from Pakistan. The reason for this lower mean age in Pakistan has been attributed to less health facilities, awareness and a lower life expectancy by the author. The commonest decade of presentation was similar to that found in Zambia (fifth decade), but higher to the Pakistan study (third and fourth decade).

A high proportion of malignancy was seen in this study (74%). The highest incidence of malignancy was in the third decade (32%). Our own earlier unpublished data on 680 well differentiated thyroid cancers (2006 – 2010) indicate a peak incidence of malignancy in the fourth decade (37%). This is contrary to literature where a peak incidence of malignancies is reported in the sixth to seventh decade in males and in the fifth decade in females (80–82). Hence we are seeing a shift in the peak incidence of thyroid cancers to an earlier decade. Possible reasons may be:

1. Improved awareness of thyroid disease in the community and earlier presentation
2. Advances in technology and multiple imaging modalities available leading to earlier detection of thyroid nodules

3. Advances in pathological diagnosis - the previously common diagnosis of follicular adenoma is now almost non-existent and is diagnosed as follicular variant of papillary carcinoma thyroid

4. Secondary to a yet unknown environmental cause

**2) Gender**

In literature goiters are more commonly seen in females. In this study as well there was a predominance of female patients presenting with goiters. The malignancy rate was higher in male patient with goitre, indicating that a thyroid nodule discovered in a male should be considered more likely to be malignant than a nodule in a female. This conclusion may not reflect the true picture as the numbers are small.

**3) Indication for operation and final histology**

Thirty one patients (62%) were operated for a suspicion/proved malignancy. The final histopathology revealed thirty six patients (72%) with carcinoma thyroid. This reflects a referral bias as we are a tertiary hospital the majority of patients we manage have malignancy.

**4) Preoperative Chvostek**

We found 16% of patients with Chvostek's sign positive preoperatively. In the postoperative period all the patients with hypocalcemia were Chvostek's positive (30%). This indicates that Chvostek's sign is more sensitive but a less specific sign of hypocalcemia. It is reported to be present in upto 10-25% of healthy adults (83).

**5) Operation performed**

Our policy is to perform total thyroidectomy for benign as well as malignant thyroid disease. With respect to malignant thyroid we do not perform prophylactic central or lateral compartment neck dissections. This reflects the statistics of operations performed wherein total thyroidectomy is the most common procedure despite there being a malignancy rate of 74%.

6) **Gland weight**

Eighty four percent of the thyroid glands resected weighed 100g or less while the remaining sixteen percent weighed more than 100g. There is a large discrepancy in the number in both arms. Hence comparison may not reveal the true position.

## B) Prevalence of hypomagnesemia (preoperative)

The prevalence of hypomagnesemia among the patients undergoing thyroidectomy was twenty four percent (twelve patients). To the best of our knowledge this is the first documentation of the prevalence of hypomagnesemia among this subset of patients in India.

This prevalence lies between the estimates of 4.6% and 14.5% in Iranian and German population and 43% among pregnant women in Haryana.

We note that all the twelve patients who were hypomagnesemic had magnesium values between 1.6 to 1.79mg/dl suggesting they were mild. There were also 10% of patients whose calcium values were below the laboratory reference range preoperatively. The dietary pattern of our population is different from the west. This may contribute to the higher prevalence of hypomagnesemia observed in our study as well as the one from Haryana. We presume that the hypomagnesemia seen in this subset of patients may be secondary to malnutrition. As we have not assessed the nutritional status of our patients we could not confirm this theory.

The study from Haryana also found a significant association between parity and hypomagnesemia, women with parity of more than two being at a higher risk of developing hypomagnesemia than nulliparous women. We have not assessed parity in our study.

There are several reports of hypomagnesemia following chronic proton pump inhibitor usage. In our country these medications are commonly dispensed over the counter. This factor was not considered preoperatively.

## C) Prevalence of hypomagnesemia (postoperative)

Our study shows that a large number of patients were hypomagnesemic following surgery, seventy percent (thirty five patients). Among these sixteen patients (46%) had a value between 1.61 - 1.8, eleven patients (31%) had a value between 1.41 - 1.6 and eight patients (23%) had a value less than 1.4mg/dl. We attribute this fall to three reasons:

1. Hemodilution

2. Hypoparathyroidism – PTH stimulates magnesium reabsorption from the kidney and small intestine. PTH also causes release of magnesium from the bone. In this study we have documented a low PTH in twenty patients postoperatively.

3. Thyrotoxicosis – All the four patients with thyrotoxicosis had hypomagnesemia postoperatively

The other possibilities for the postoperative hypomagnesemia include severe vomiting and diarrhea postoperatively, uncontrolled blood sugars and in alcoholics. These factors were not assessed.

## D) Role of magnesium in post thyroidectomy hypocalcemia

The role of magnesium in post thyroidectomy hypocalcemia was proposed to be in the "persistent hypocalcemia" subset of patients. This subset of patients was not well captured in this study. There were only three patients who required intravenous correction of calcium/magnesium. The details of these three patients are given below.

### i) Persistent hypocalcemia – patient 1

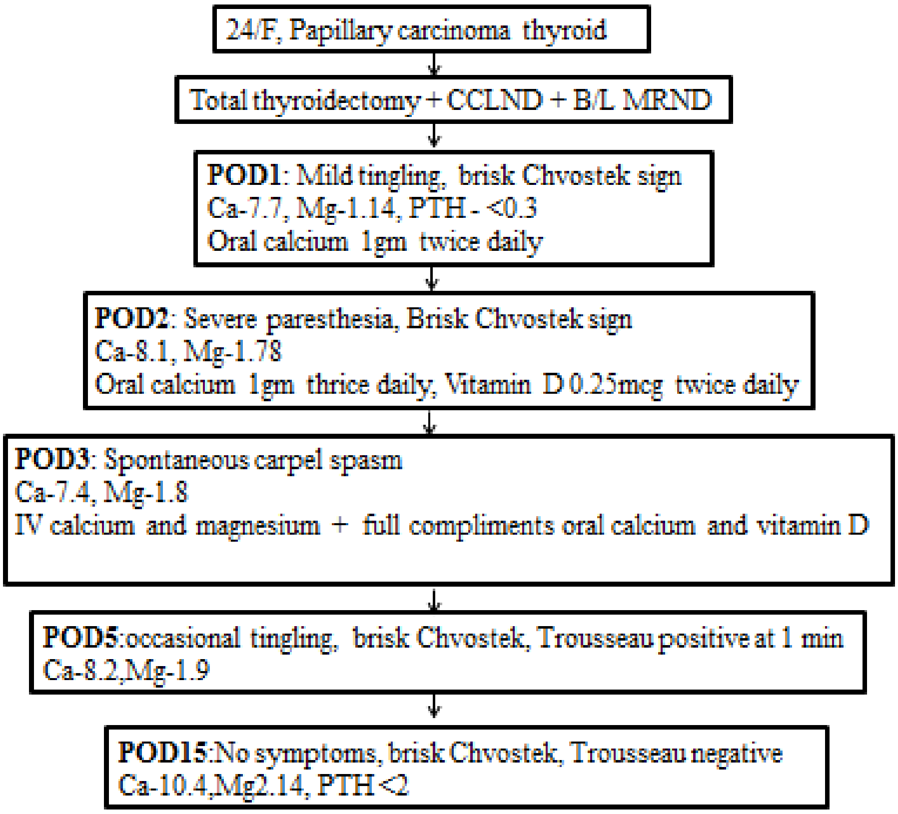
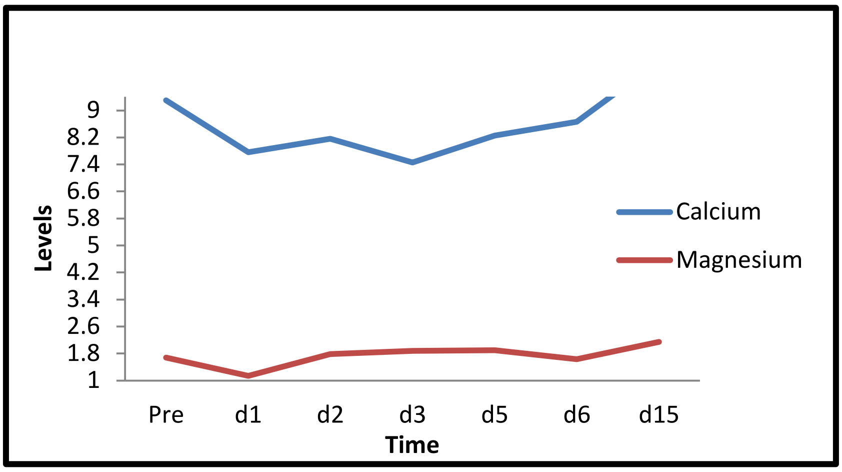
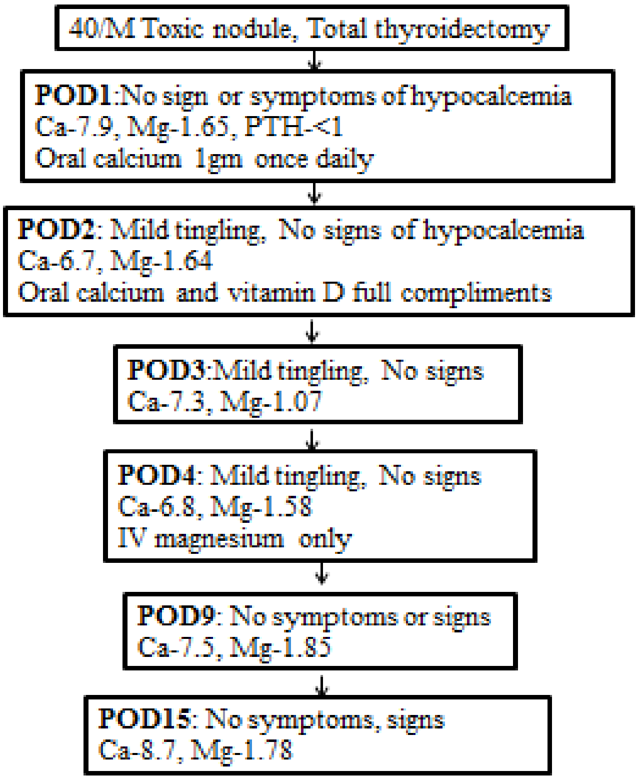


**Figure 34: Calcium and magnesium values**



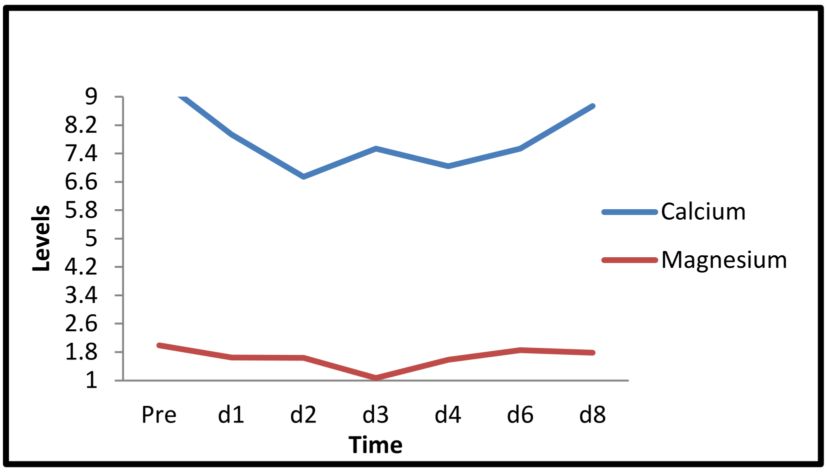

In this patient three parathyroid glands were seen and preserved intraoperatively. Hence parathyroid status is probably not the cause of hypocalcemia in this patient. Her symptoms of hypocalcemia worsened and there was a biochemical fall in calcium in spite of oral calcium supplementation. Serum magnesium was low in the postoperative period. Correction of magnesium resulted in improvement of symptoms and biochemical value of calcium. Hence we demonstrate a possible relationship between hypomagnesemia and hypocalcemia.

### ii) Persistent hypocalcemia – patient 2



This patient with a toxic nodule of the thyroid had an elevated alkaline phosphatase level preoperatively (204U/L). All four parathyroid gland were identified and preserved intraoperatively. The cause of hypocalcemia postoperative can be debated as being secondary to hungry bone syndrome or hypomagnesemia.

**Figure 35: Calcium and magnesium values**




The persistent hypocalcemia witnessed in both cases above were in patients at risk of developing hypocalcemia postoperatively.

### iii) Delayed hypocalcemia – patient 1

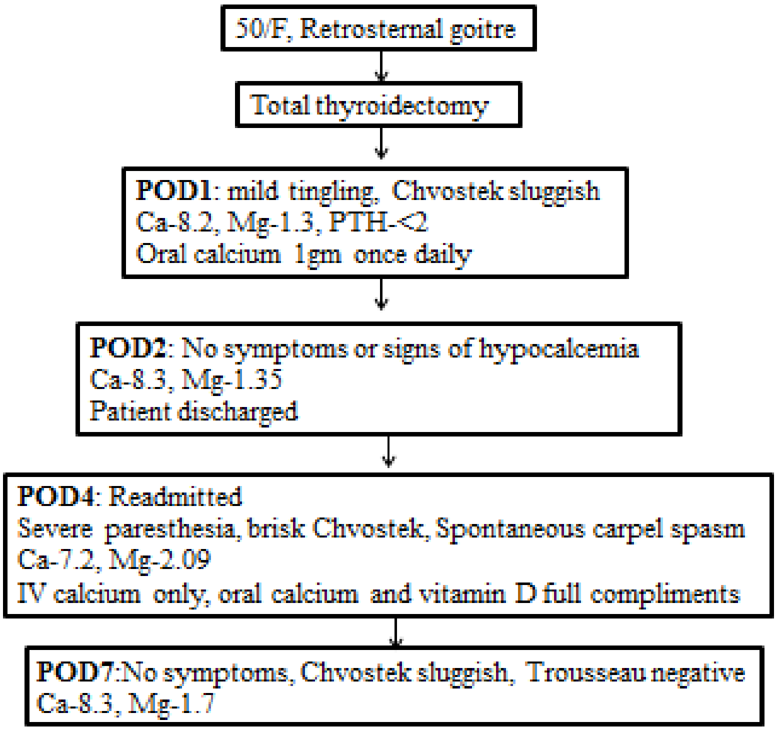
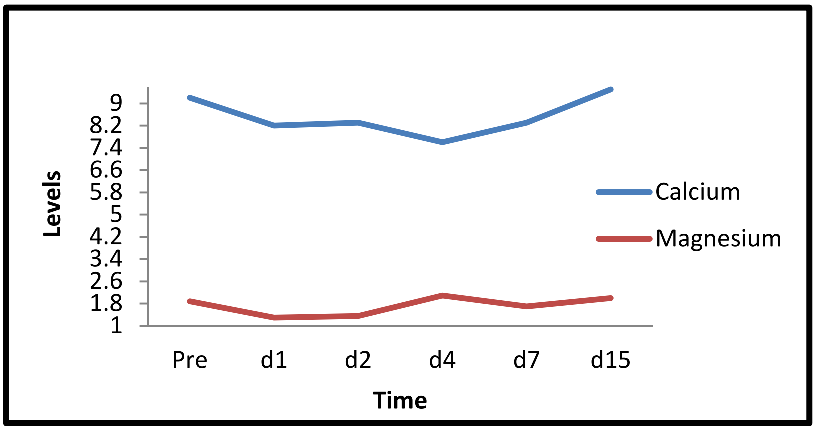


**Figure 36: Calcium and magnesium values**




This patient had one parathyroid autotransplanted intraoperatively. The hypocalcemia in this patient may have been secondary to a parathyroid related cause.

## Other factors implicated in post thyroidectomy hypocalcemia

### 1) Age and gender

There are reports of increasing age (>50 years) and female gender being risk factors to develop hypocalcemia following thyroidectomy. We did not see such trends. Thirty five patients (70%) in our study were less than fifty years of age and this may be the reason for our findings.

### 2) Vitamin D

A strong relationship between vitamin D and hypocalcemia, low vitamin D being a risk factor for post thyroidectomy hypocalcemia is observed in literature (3,62). Interestingly, our results indicate a contrary finding suggestive of a protective effect of preoperative hypovitaminosis D, which was statistically significant (p=0.03). A similar result was observed in previous unpublished work evaluating vitamin D and hypocalcemia at our department. We hypothesize that the possible explanation for this association is that a low vitamin D level causes a secondary hyperparathyroid state, stimulating the parathyroid glands to secrete PTH and hence keeping the calcium levels elevated. Further evaluation with a larger number of patients is required to prove this finding.

**3) Thyrotoxicosis**

We had three patients with Graves' disease and two with a toxic nodule of the thyroid. We did not find an association between presence of toxicity and hypocalcemia. Two out of the three patients had a transient hypocalcemia (corrected with oral calcium alone in two days). These two patients also had a mild fall in magnesium postoperatively. In both patients their alkaline phosphatase values were normal. Considering the above facts, the cause of hypocalcemia in these two patients could be attributed to hemodilution. Only one patient had an elevated alkaline phosphatase and developed symptomatic hypocalcemia requiring IV magnesium. As this patient had an elevated alkaline phosphatase, hungry bone syndrome is implicated as the cause of hypocalcemia. These numbers are too small to make any statistical conclusions regarding the risk of developing hypocalcemia secondary to thyrotoxicosis.

However, we did observe that among the patients with elevated alkaline phosphatase, seventy one percent developed hypocalcemia. This may indicate that a high alkaline phosphatase is a marker to predict the development of postoperative hypocalcemia. Here again the total number was too small (seven patients) to draw any conclusions.

**4) Parathyroid status**

We used PTH as a surrogate marker of parathyroid injury. As was expected we found a strong correlation between low PTH (<8pg/ml) and the development of hypocalcemia.

We also observed that among the thirty patients with a normal PTH postoperatively, six (20%) developed hypocalcemia. Four of these patients (67%) had hypomagnesemia. Among the twenty patients with low PTH, eleven (55%) had normal calcium. Nine of these patients (82%) had hypomagnesemia. Hence it seems that parathyroid injury alone was not responsible for the hypocalcemia witnessed in our patients. Hypomagnesemia also seems to be related to both hypoparathyroidism and hypocalcemia. This indicates that the etiology of post thyroidectomy hypocalcemia is complex and simplistic replacement solutions may not produce uniform results.

**5) Volume of fluids used**

Our study showed a direct correlation between amount of fluids used and postoperative hypocalcemia, which is again similar to documentation in literature. This shows that hemodilution is one of the main factors responsible for the development of hypocalcemia postoperatively.

**6) Extent of dissection**

Contrary to literature, we did not find a significant association between the extent of dissection and development of hypocalcemia. Greater extent of dissection is expected to be associated with a higher risk of injury to the parathyroid glands and also inadvertent parathyroidectomy (in patients undergoing central compartment clearance). There were no parathyroid glands reported in the final histopathology for any of the patients. We are in the habit of recording the parathyroid status intraoperatively, do not perform prophylactic central neck dissection and do not routinely autotransplant the inferior parathyroid during therapeutic central compartment dissection. This may have contributed to the precaution exercised in preserving the parathyroid glands.

**7) Duration of operation**

Fifty percent of the operations performed were completed within ninety minutes. A further twenty eight percent were completed in 120 minutes. This is a short duration for surgery. This is possibly the reason for our result of no significant association between the duration of surgery and the development of hypocalcemia.

# Conclusion

1) The **prevalence of hypomagnesemia is 24%** preoperatively in this cohort of patients. They were all mild deficiency 1.6 to 1.8. **Vitamin D deficiency (< 20) was 62%.**

2) The **postoperative hypocalcemia (calcium <8mg/dl) rate was 30%**. **Hypovitaminosis D appeared to protect against postoperative hypocalcemia**; this finding is at variance with published literature.

3) There was a **marked rise in postoperative hypomagnesemia (70%).** A **similar pattern of fall in calcium and magnesium following thyroid surgery** which normalized by one to two weeks without intravenous correction was observed.

4) **Hemodilution and low PTH** were significantly associated with post thyroidectomy hypocalcemia. The ROC curve showed that a PTH of 4.1-6pg/ml was the best predictor of hypocalcemia.

5) The cause of hypocalcemia post thyroidectomy in this study is mainly a factor of parathyroid function and fluid status. Magnesium levels tend to mimic the calcium levels postoperatively and there is possibly an association rather than a causation. This study therefore does not prove or disprove the role of magnesium supplementation to help correct postoperative hypocalcemia.

# Future direction

This study has led us to consider the following two studies to further evaluate the role of magnesium in post thyroidectomy hypocalcemia.

For the patients with persistent hypocalcemia and associated hypomagnesemia, we propose a randomized study of correction versus no correction of hypomagnesemia and evaluate the calcium response.

Secondly, we propose a study to identify patients at risk of developing persistent hypocalcemia, checking their magnesium levels preoperatively and if low correcting it in the perioperative period to see if this prevents persistent postoperative hypocalcemia.

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# Annexure - 1

## CONSENT FORM

Study Title: Role of magnesium in post thyroidectomy hypocalcemia.

Study Number:

Patient Name:

Hospital number:

I, son/daughter of

Declare that I have read the information sheet provided to me regarding this study and have clarified any doubts that I have had.

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights.

I understand that I will not receive any other financial compensation.

I understand that my identity will not be relieved in any information released to third parties or published.

I voluntarily agree to take part in this study.

| | |
|---|---|
| Name: | Name and signature of witness: |
| Signature: | Relation to participant: |
| Date: | Date: |

# Annexure - 2

DEPARTMENT OF ENDOCRINE SURGERY

CHRISTIAN MEDICAL COLLEGE AND HOSPITAL, VELLORE

## PATIENT INFORMATION SHEET

Thyroid disorders are common in India. Many of these patients require surgery in the form of removal of the thyroid gland as their treatment. This is associated with many complications even in the best of hands. Hypocalcemia – decreased blood level of calcium, is the most common complication. Patients with hypocalcemia complain of numbness/tingling sensation around their mouth or in their hands and feet. Severe hypocalcemia could even result in spontaneous cramping of fingers. Majority of these patients symptoms resolve with calcium and vitamin D supplementation. A subset of patients who do not resolve are termed to have persistent hypocalcemia. It is postulated that in this subset of patients magnesium plays a role in the refractoriness of hypocalcemia. If this is proved, correction of magnesium may be used to treat persistent hypocalcemia. If a critical preoperative magnesium level is identified, prophylactic magnesium may be administered to prevent post thyroidectomy hypocalcemia. We therefore propose to carry out a study to determine if there is a significant drop in magnesium levels after thyroid surgery and to assess the role of magnesium in post thyroidectomy hypocalcemia

**If you take part what will you have to do?**

Blood samples will be taken prior to surgery as well as on all days of hospitalisation after operation. Signs and symptoms of hypocalcemia will be checked postoperatively. This is routinely performed on all patients not part of this study as well.

**Can you withdraw from this study?**

Your participation in this study is entirely voluntary and you are free to withdraw at any time. If you do so this will not affect your usual treatment at the hospital in any way.

**Will there be any additional cost to participate in this study?**

No

**What happens after this study is over?**

You may not benefit from this study, however it might later benefit patients who develop or are at risk of developing post thyroidectomy hypocalcemia.

**Will your personal details be kept confidential?**

The result of this study will be published in a medical journal but you will not be identified by name in any publication or presentation. However your medical notes may be reviewed by people associated with the study, without you additional permission, should you decide to participate in this study.

# Annexure – 3

DATA SHEET

| | hno | age | gender | indsur | ifbeni | sighypo | chvosys | prca | pralb | prmg | prp | prvitd | prpth | prealkp | opper | parathst | numseen | numpres | numautot | durope | volflu | wtthygl | symhypo | d1occting | d1sevpares | d1mldcram | d1sevcram |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 249916F | 25 | 2 | 3 | | 1 | 1 | 8.9 | 4 | 2.07 | 2.9 | 10.8 | 58 | 65 | 3 | | 2 | 2 | 0 | 180 | 3000 | 60 | 1 | 2 | 2 | 2 | 2 |
| 2 | 254320F | 24 | 2 | 3 | | 2 | | 7.8 | 4.4 | 1.71 | 2.4 | 15.18 | 16.8 | 117 | 1 | | 4 | 4 | 0 | 90 | 2000 | 20 | 2 | 2 | 2 | 2 | 2 |
| 3 | 994025D | 69 | 2 | 1 | 4 | 2 | | 8.6 | 4.6 | 2.11 | 4 | 13.69 | 100.2 | 102 | 1 | | 3 | 2 | 1 | 180 | 2500 | 300 | 2 | 2 | 2 | 2 | 2 |
| 4 | 260837F | 40 | 1 | 2 | | 1 | 1 | 8.1 | 4.8 | 2.13 | 2.7 | 10.2 | 63.2 | 97 | 1 | | 4 | 4 | 0 | 105 | 2000 | 25 | 2 | 2 | 2 | 2 | 2 |
| 5 | 337337F | 47 | 1 | 3 | | 2 | | 8.1 | 4.6 | 2.3 | 2.7 | 12.67 | 88 | 130 | 3 | | 2 | 2 | 0 | 180 | 1500 | 30 | 2 | 2 | 2 | 2 | 2 |
| 6 | 270535F | 42 | 1 | 1 | | 1 | 1 | 8.3 | 4.6 | 2.22 | 3.4 | 25.5 | 40.2 | 107 | 5 | | 2 | 2 | 0 | 180 | 2000 | 25 | 2 | 2 | 2 | 2 | 2 |
| 7 | 335713F | 30 | 2 | 3 | | 2 | | 8.5 | 4.9 | 2.12 | 2.1 | 22.7 | 54.4 | 86 | 1 | | 3 | 3 | 0 | 90 | 2500 | 25 | 1 | 2 | 2 | 2 | 2 |
| 8 | 256589F | 41 | 1 | 3 | | 2 | | 8.4 | 4.9 | 1.86 | 3.2 | 14.06 | 76.5 | 87 | 3 | | 3 | 2 | 1 | 150 | 1500 | 20 | 2 | 2 | 2 | 2 | 2 |
| 9 | 267713F | 47 | 2 | 1 | | 2 | | 8.86 | 3.8 | 1.94 | 3.9 | 18.07 | 46 | 95 | 1 | | 3 | 2 | 1 | 90 | 1500 | 25 | 2 | 2 | 2 | 2 | 2 |
| 10 | 236789F | 54 | 2 | 1 | 3 | 2 | | 9.02 | 4.1 | 1.75 | 3.2 | 9.74 | 91 | 88 | 1 | | 4 | 4 | 0 | 90 | 2000 | 25 | 2 | 2 | 2 | 2 | 2 |
| 11 | 307632F | 50 | 2 | 1 | 3 | 2 | | 8.58 | 4.4 | 1.78 | 3.6 | 15.6 | 91.9 | 96 | 1 | | 4 | 4 | 0 | 90 | 2000 | 20 | 2 | 2 | 2 | 2 | 2 |
| 12 | 266209F | 69 | 2 | 2 | | 2 | | 10.06 | 4.3 | 1.71 | 2.6 | 16.57 | 164 | 164 | 1 | | 4 | 3 | 0 | 90 | 2000 | 50 | 2 | 2 | 2 | 2 | 2 |
| 13 | 263024F | 46 | 2 | 2 | | 2 | | 9.02 | 4.6 | 1.84 | 4.1 | 34.45 | 50.2 | 94 | 1 | | 3 | 3 | 0 | 110 | 2500 | 25 | 2 | 2 | 2 | 2 | 2 |
| 14 | 324629F | 54 | 1 | 3 | | 2 | | 9.18 | 3.9 | 1.95 | 2.6 | 27.4 | 93.7 | 88 | 1 | | 3 | 3 | 0 | 120 | 2000 | 120 | 2 | 2 | 2 | 2 | 2 |
| 15 | 670207D | 40 | 2 | 2 | | 2 | | 8.42 | 4.6 | 2.54 | 3.5 | 29.02 | 81 | 59 | 1 | | 4 | 4 | 0 | 110 | 2000 | 70 | 2 | 2 | 2 | 2 | 2 |
| 16 | 289870F | 27 | 1 | 3 | | 2 | | 8 | 4.5 | 1.9 | 2.8 | 14.7 | 40.6 | 82 | 2 | | 4 | 3 | 1 | 195 | 2500 | 50 | 2 | 2 | 2 | 2 | 2 |
| 17 | 175170F | 40 | 1 | 1 | 2 | 2 | | 9.42 | 4.1 | 1.99 | 3.3 | 33.48 | 45.9 | 209 | 1 | | 4 | 4 | 0 | 60 | 2500 | 20 | 1 | 2 | 2 | 2 | 2 |
| 18 | 329255C | 48 | 2 | 1 | | 2 | | 8.78 | 3.9 | 2.8 | 2.8 | 20.8 | 86 | 81 | 5 | | 1 | 1 | 0 | 75 | 2500 | 8 | 2 | 2 | 2 | 2 | 2 |
| 19 | 306217C | 33 | 2 | 2 | | 1 | 1 | 8.52 | 4.1 | 2.07 | 4.3 | 19 | 57.9 | 80 | 1 | | 2 | 2 | 0 | 105 | 2500 | 130 | 1 | 2 | 2 | 2 | 2 |
| 20 | 274501F | 30 | 2 | 1 | 1 | 2 | | 8.68 | 4.4 | 1.77 | 3.9 | 19.67 | 7.1 | 8.1 | 1 | | 3 | 2 | 1 | 130 | 2500 | 25 | 2 | 2 | 2 | 2 | 2 |
| 21 | 283252F | 30 | 2 | 2 | | 2 | | 8.3 | 4.5 | 1.81 | 3.4 | 14.91 | 28.9 | 81 | 1 | | 4 | 4 | 0 | 70 | 3000 | 15 | 1 | 1 | 2 | 2 | 2 |
| 22 | 283311F | 37 | 2 | 1 | 3 | 1 | 1 | 8.3 | 4.5 | 1.92 | 3.6 | 12.51 | 14.6 | 59 | 1 | | 4 | 4 | 0 | 110 | 2500 | 20 | 2 | 2 | 2 | 2 | 2 |
| 23 | 318885F | 18 | 2 | 3 | | 2 | | 9.06 | 4.8 | 1.92 | 3.9 | 18.12 | 0.5 | 83 | 3 | | 4 | 2 | 2 | 165 | 2500 | 10 | 1 | 1 | 2 | 2 | 2 |
| 24 | 069349D | 21 | 2 | 1 | 2 | 2 | | 9.06 | 4.3 | 1.73 | 2.8 | 19.1 | 20.8 | 115 | 1 | | 3 | 3 | 0 | 90 | 2500 | 100 | 2 | 2 | 2 | 2 | 2 |
| 25 | 274329F | 21 | 2 | 2 | | 1 | 2 | 8.62 | 4.6 | 1.96 | 3.7 | 26.76 | 54.5 | 81 | 1 | | 4 | 4 | 0 | 90 | 2000 | 15 | 2 | 2 | 2 | 2 | 2 |
| 26 | 262931F | 65 | 2 | 1 | 2 | 2 | | 8.94 | 4.7 | 1.89 | 4.4 | 20.8 | 49.9 | 118 | 1 | | 4 | 4 | 0 | 90 | 2000 | 30 | 2 | 2 | 2 | 2 | 2 |
| 27 | 350247F | 55 | 2 | 1 | 1 | 2 | | 8.62 | 4.1 | 2.18 | 3.7 | 20.93 | 18.5 | 76 | 1 | | 4 | 3 | 1 | 150 | 2500 | 140 | 2 | 2 | 2 | 2 | 2 |
| 28 | 277185F | 33 | 2 | 1 | 1 | 2 | | 8.94 | 4.2 | 1.68 | 3 | 16.39 | 55.4 | 80 | 1 | | 4 | 4 | 0 | 120 | 2500 | 170 | 1 | 1 | 2 | 2 | 2 |
| 29 | 321878F | 45 | 2 | 3 | | 2 | | 8 | 4.2 | 2.14 | 3.4 | 35.24 | 119.4 | 138 | 1 | | 4 | 4 | 0 | 90 | 2500 | 25 | 1 | 1 | 2 | 2 | 2 |
| 30 | 273851F | 30 | 2 | 2 | | 2 | | 8.8 | 4.4 | 1.7 | 3.1 | 24.5 | 87.9 | 62 | 1 | | 4 | 4 | 0 | 90 | 2500 | 25 | 2 | 2 | 2 | 2 | 2 |
| 31 | 350236F | 51 | 1 | 3 | | 2 | | 9.16 | 4.3 | 1.71 | 2.9 | 29.42 | 21.2 | 97 | 1 | | 4 | 4 | 0 | 120 | 2000 | 240 | 1 | 2 | 2 | 2 | 2 |
| 32 | 267827F | 42 | 1 | 3 | | 2 | | 8.3 | 5 | 2.02 | 3.1 | 17.3 | 152.6 | 142 | 4 | | 4 | 3 | 1 | 120 | 3000 | 50 | 2 | 2 | 2 | 2 | 2 |
| 33 | 274757F | 49 | 2 | 1 | 2 | 2 | | 8.82 | 3.6 | 1.81 | 4.1 | 43.45 | 20.8 | 76 | 1 | | 3 | 3 | 0 | 120 | 3500 | 110 | 1 | 1 | 2 | 2 | 2 |
| 34 | 289960F | 52 | 2 | 2 | | 2 | | 8.48 | 4.9 | 2.32 | 3.9 | 14.1 | 23.4 | 102 | 1 | | 4 | 4 | 0 | 120 | 2000 | 20 | 2 | 2 | 2 | 2 | 2 |
| 35 | 260870F | 34 | 2 | 1 | 1 | 1 | 1 | 9.5 | 4 | 2.09 | 4.2 | 34.6 | 66.9 | 51 | 1 | | 2 | 2 | 0 | 90 | 2500 | 125 | 2 | 2 | 2 | 2 | 2 |
| 36 | 319242F | 43 | 1 | 1 | 1 | 2 | | 8.42 | 4.6 | 2.15 | 3.1 | 13.7 | 104.1 | 86 | 2 | | 3 | 2 | 1 | 120 | 4000 | 50 | 1 | 2 | 2 | 2 | 2 |
| 37 | 308045F | 44 | 2 | 2 | | 2 | | 8.88 | 4.4 | 2.56 | 3.7 | 15.69 | 54.7 | 104 | 1 | | 4 | 3 | 1 | 110 | 2500 | 50 | 2 | 2 | 2 | 2 | 2 |
| 38 | 306307F | 26 | 2 | 2 | | 2 | | 8.92 | 4.6 | 2.65 | 3.7 | 24.9 | 32.3 | 92 | 1 | | 4 | 4 | 0 | 90 | 3000 | 50 | 2 | 2 | 2 | 2 | 2 |
| 39 | 279820F | 27 | 2 | 2 | | 2 | | 8.76 | 4.8 | 1.85 | 2.3 | 10.68 | 57 | 67 | 2 | | 4 | 4 | 0 | 75 | 1500 | 25 | 2 | 2 | 2 | 2 | 2 |
| 40 | 216650F | 53 | 1 | 1 | 2 | 2 | | 9.38 | 3.9 | 2.34 | 4.3 | 15.59 | 91 | 85 | 1 | | 2 | 2 | 0 | 90 | 1500 | 50 | 2 | 2 | 2 | 2 | 2 |
| 41 | 303715F | 24 | 2 | 2 | | 1 | 2 | 8.5 | 5 | 1.68 | 3 | 23.4 | 68.3 | 80 | 4 | | 3 | 3 | 0 | 180 | 3000 | 20 | 1 | 1 | 2 | 2 | 2 |
| 42 | 301677F | 55 | 2 | 2 | | 2 | | 8.88 | 4.4 | 1.88 | 3.4 | 10.5 | 61.3 | 149 | 1 | | 3 | 2 | 1 | 110 | 2500 | 75 | 1 | 1 | 2 | 2 | 2 |
| 43 | 317665F | 48 | 2 | 1 | | 2 | | 9.04 | 4.7 | 2.25 | 4 | 18.3 | 57.5 | 88 | 1 | | 1 | 1 | 0 | 90 | 2500 | 15 | 2 | 2 | 2 | 2 | 2 |
| 44 | 308630F | 24 | 2 | 1 | 1 | 2 | | 8.76 | 4.3 | 1.6 | 3.6 | 10 | 72.3 | 77 | 1 | | 4 | 4 | 0 | 90 | 2000 | 100 | 2 | 2 | 2 | 2 | 2 |
| 45 | 403165F | 75 | 2 | 3 | | 2 | | 8.18 | 3.9 | 2.66 | 4.1 | 21.53 | 43.3 | 89 | 2 | | 1 | 0 | 1 | 100 | 2000 | 10 | 1 | 1 | 2 | 2 | 2 |
| 46 | 278925F | 36 | 2 | 2 | | 2 | | 8.4 | 4.5 | 1.62 | 2.6 | 14.7 | 64.6 | 85 | 1 | | 3 | 3 | 0 | 60 | 2000 | 100 | 2 | 2 | 2 | 2 | 2 |
| 47 | 314477F | 61 | 2 | 2 | | 2 | | 8.76 | 4.8 | 2.17 | 3.4 | 15.62 | 118 | 160 | 1 | | 2 | 2 | 0 | 90 | 2000 | 100 | 2 | 2 | 2 | 2 | 2 |
| 48 | 339600F | 51 | 2 | 1 | 1 | 2 | | 8.3 | 4.4 | 1.93 | 3.8 | 15.97 | 48 | 94 | 1 | | 4 | 3 | 1 | 110 | 2500 | 75 | 2 | 2 | 2 | 2 | 2 |
| 49 | 432151F | 51 | 1 | 3 | | 2 | | 9.34 | 5.2 | 2 | 3.9 | 22.9 | 62.1 | 108 | 3 | | 2 | 2 | 0 | 180 | 2000 | 40 | 2 | 2 | 2 | 2 | 2 |
| 50 | 444740F | 68 | 1 | 3 | | 2 | | 9.3 | 4.5 | 2.48 | 3.5 | 21.2 | 20.1 | 87 | 3 | | 2 | 2 | 0 | 180 | 2500 | 20 | 2 | | | | |

| d2occting | d2evparest | d2mldcram | d2sevcram | d3occting | d3evparest | d3mldcram | d3sevcram | d4occting | d4evparest | d4mldcram | d4sevcram | d5occting | d5evparest | d5mldcram | d5sevcram | d6occting | d6evparest | d6mldcram | d6sevcram | d7occting | d7evparest | d7mldcram | d7sevcram | d8occting | d8evparest | d8mldcram | d8sevcram |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 1 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 1 | 2 | 2 | 2 | | 1 | 2 | 2 | | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 1 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 1 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 1 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 1 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | |
| 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 |
| 2 | 2 | 2 | 2 | | | | | | | | | | | | | 2 | 2 | 2 | 2 | | | | | | | | |

| d9occting | d9evparest | d9mldcram | d9sevcram | d15occting | d15evpare | d15mldcrai | d15sevcrar | sighypo1 | d1chvost | d1trouspostime1 | d2chvost | d2trouspostime2 | d3chvost | d3trouspostime3 | | d4chvost | d4trouspostime4 | | d5chvost | d5trouspostime5 | | d6chvost | d6trouspostime6 | d7chvost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 2 | 2 | 2 | 2 | 2 | | | | | | | | | | 2 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 1 | 2 | 1 | 2 | | | | | | | | | | 1 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | 0 | 2 | | | | |
| | | | | | | | | 1 | 1 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | 0 | 2 | | 0 | 2 | | 0 | 2 | | 0 | 2 | 0 |
| | | | | | | | | 1 | 1 | 2 | 1 | 2 | | | | 1 | 2 | | | | | | | |
| | | | | | | | | 1 | 1 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | 0 | 2 | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 1 | 2 | 1 | 2 | | | | 1 | 2 | | | | | | | |
| 2 | 2 | 2 | 2 | | | | | 2 | 0 | 2 | 0 | 2 | 0 | 2 | | 0 | 2 | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | | | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 1 | 2 | 1 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 2 | 2 | 2 | 2 | | | | 2 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 1 | 2 | 2 | 2 | 2 | | | | | | | | | | | | 2 |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | 0 |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | 0 | 2 | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 0 | 2 | 0 | 2 | | | | 1 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | 0 |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | 0 | 2 | | | | |
| | | | | | | | | 1 | 2 | 2 | 2 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 2 | 2 | 2 | 2 | | | | | | | | | | 2 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | |
| | | | | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 30 | 1 | 1 | 30 | 1 | 1 | 60 | 1 | 2 | |
| | | | | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 0 | 2 | | | | 2 | 1 | 0 | 2 | 1 | 30 | 1 | 2 | 1 |
| | | | | | | | | 1 | 1 | 2 | 1 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 1 | 1 | 2 | 0 | 2 | | | | 0 | 2 | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | | | |
| | | | | | | | | 2 | 0 | 2 | 0 | 2 | | | | | | | | | | 0 | 2 | |
| | | | | | | | | 2 | | | | | | | | | | | | | | | | |

| d7trouspostime7 | d8chvost | d8trouspostime8 | d9chvost | d9trouspostime9 | d15chvost | d15trouspostime15 | d1ca | d1alb | d1mg | d1p | d1vitd | d1pth | d1ealkp | d2ca | d2alb | d2mg | d2p | d2vitd | d2pth | d2ealkp | d3ca | d3alb | d3mg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 6.9 | 3.8 | 1.66 | 2.8 | | 20 | | 7.4 | | 1.76 | 3 | | | | 7.2 | | |
| | | | | | | | 8.8 | 4 | 1.7 | 3.2 | | 19.7 | | 8 | | 1.9 | 2.7 | | | | | | |
| | | | | | | | 7.9 | 3.3 | 1.69 | 4.2 | | 25.1 | | 7.8 | | 2.1 | 3.8 | | | | | | |
| | | | | | | | 8.6 | 3.7 | 1.78 | 3.4 | | 17.7 | | 8.8 | | 1.97 | 3.4 | | | | | | |
| | | | | | | | 8.06 | 3.8 | 1.8 | 2 | | 43.3 | | 9.1 | | 1.9 | 2.1 | | | | | | |
| | | | | | | | 7.5 | 3.7 | 2.12 | 2.7 | | 19.7 | | 8.5 | | 2.1 | 2.8 | | | | | | |
| 2 | | | | | | | 8.5 | 3.8 | 1.7 | 3.5 | | 4.6 | | 8.5 | | 1.5 | 3.8 | | | | 7.3 | | 1.5 |
| | | | | | | | 8.8 | 3.5 | 1.6 | 4 | | 0.5 | | 8.4 | | 1.44 | 4.1 | | | | | | |
| | | | | | | | 7.9 | 3.6 | 1.65 | 3.9 | | 35.8 | | 8.9 | | 1.9 | 4.4 | | | | | | |
| | | | | | | | 9.16 | 3.3 | 1.8 | 3.8 | | 113 | | 10.3 | | 1.86 | 6.5 | | | | | | |
| | 0 | 2 | | | | | 8.5 | 3.5 | 1.75 | 3.9 | | 23.5 | | 8.7 | | 1.95 | 3.9 | | | | | | |
| | 0 | 2 | | | | | 8.5 | 3.5 | 1.49 | 2.3 | | 3.6 | | 8.9 | | 1.2 | 3.9 | | | | | | |
| | | | | | | | 9.06 | 3.8 | 1.92 | 3.8 | | 41 | | 9.46 | | 1.6 | 4.9 | | | | | | |
| | | | | | | | 8.5 | 3.8 | 1.91 | 3 | | 26.5 | | 8.2 | | 1.34 | 3.7 | | | | | | |
| | | | | | | | 8.8 | 3.9 | 1.66 | 4.9 | | 35.1 | | 8.5 | | 1.31 | 4 | | | | 8.6 | 3.8 | 1.9 |
| | 0 | 2 | | | | | 8.5 | 4.4 | 2.28 | 2.2 | | 5.9 | | 8.1 | | 1.7 | 4 | | | | | | |
| | 0 | 2 | | | | | 7.9 | 3.7 | 1.65 | 4.3 | | 1 | | 6.7 | | 1.64 | 4.5 | | | | 7.5 | | 1.07 |
| | | | | | | | 8.8 | 3.5 | 2.13 | 2.3 | | 85 | | | | | | | | | | | |
| | | | | | | | 8.5 | 3.6 | 1.7 | 4.3 | | 17 | | 7.3 | | 1.74 | 4.3 | | | | | | |
| | | | | | | | 8.2 | 4 | 1.6 | 4.4 | | 1 | | 8.1 | | 1.51 | 5.7 | | | | | | |
| | | | | | | | 7.6 | 3.7 | 1.92 | 2.8 | | 3.1 | | 8.9 | | 1.71 | 3.5 | | | | | | |
| | | | | | | | 8.1 | 3.5 | 1.48 | 3.5 | | 17.5 | | 9.4 | | 1.77 | 3.5 | | | | | | |
| | | | | | | | 8.7 | 3.7 | 1.68 | 4.2 | | 8.3 | | 9.04 | | 1.61 | 5.5 | | | | | | |
| | | | | | 0 | 2 | 7.1 | 3.5 | 1.6 | 4.4 | | 1.5 | | 7.8 | | 3.4 | 4.3 | | | | | | |
| 2 | | | | | | | 8.7 | 3.8 | 1.48 | 3.7 | | 40.5 | | 8.3 | | 1.8 | 4.2 | | | | | | |
| 2 | | | | | | | 8.2 | 3.8 | 1.2 | 4.7 | | 17.7 | | 8.2 | | 1.7 | 4.5 | | | | | | |
| | | | | | | | 7.9 | 3.8 | 1.49 | 3.7 | | 1.5 | | 7.7 | | 2.08 | 3.6 | | | | 8 | | 1.67 |
| | | | | | | | 8.6 | 3.5 | 1.35 | 3.3 | | 31 | | 10 | | 1.36 | 3.2 | | | | | | |
| | | | | | | | 7.6 | 3.4 | 1.34 | 3.4 | | 3 | | 8.2 | | 1.7 | 3.7 | | | | | | |
| | | | | | | | 8.4 | 3.3 | 1.41 | 3.5 | | 32.6 | | 9 | | 1.39 | 4.1 | | | | | | |
| | | | | | | | 8.4 | 3.5 | 1.55 | 4.1 | | 0.1 | | 8.9 | | 1.61 | 4.9 | | | | | | |
| | | | | | | | 7.8 | 4 | 2.16 | 3.8 | | 14.6 | | 8.9 | | 2.12 | 4.8 | | | | | | |
| 2 | | | | | | | 7.7 | 3.3 | 1.4 | 3 | | 2 | | 8.2 | | 1.29 | 4.8 | | | | | | |
| | | | | | | | 8.2 | 3.6 | 2.1 | 4.3 | | 18.6 | | 10.3 | | 2.3 | 5 | | | | | | |
| | 1 | 2 | | | | | 7.7 | 3.5 | 1.63 | 3.5 | | 2 | | 7.7 | | 1.98 | 4.3 | | | | | | |
| | | | | | | | 8.3 | 3.9 | 1.89 | 3.3 | | 33 | | 7.9 | | 1.67 | 3.7 | | | | | | |
| | | | | | | | 8.4 | 3.9 | 2.86 | 3.4 | | 2 | | 7.8 | | 1.96 | 3.3 | | | | | | |
| | | | | | | | 8.9 | 3.9 | 2.8 | 5.4 | | 18 | | 8.4 | | 1.96 | 4.2 | | | | | | |
| | 0 | 2 | | | | | 8.7 | 4 | 1.66 | 4.1 | | 17 | | 8.4 | | 2.4 | 3 | | | | | | |
| | | | | | | | 8.6 | 3 | 1.63 | 3.5 | | 79.4 | | 9.3 | | 1.7 | 4 | | | | | | |
| | | | | | 2 | 2 | 7.7 | 3.8 | 1.14 | 4.5 | | 0.3 | | 8.1 | | 1.78 | 4.6 | | | | 7.4 | | 1.88 |
| 2 | | | | | 1 | 2 | 8.2 | 3.5 | 1.3 | 3.3 | | 2 | | 8.3 | | 1.35 | 3.1 | | | | | | |
| | | | | | | | 8.6 | 3.5 | 1.55 | 4.3 | | 2 | | 8.5 | | 1.44 | 4.4 | | | | | | |
| | | | | | | | 8.3 | 3.8 | 1.1 | 5 | | 6.8 | | 7.9 | | 1.45 | 4.8 | | | | | | |
| | | | | | | | 7.6 | 3.9 | 1.77 | 4.2 | | 2 | | 7.8 | | 1.76 | 4 | | | | | | |
| | 0 | 2 | | | | | 9.4 | 4.5 | 1.51 | 1.9 | | 14.4 | | 8.7 | | 1.4 | 3.9 | | | | | | |
| | 0 | 2 | | | | | 7.9 | 3.6 | 1.74 | 4.7 | | 45 | | 8.7 | | 1.6 | 3.2 | | | | | | |
| | 0 | 2 | | | | | 8.1 | 3.4 | 1.58 | 4.9 | | 9.3 | | 8.1 | | 1.57 | 4.1 | | | | | | |
| | | | | | | | 8.8 | 4.6 | 1.8 | 3.6 | | 17.4 | | 8.7 | | 2.17 | 4.4 | | | | | | |
| | | | | | | | 8.7 | 3 | 2.31 | 4.8 | | 6.1 | | 9.2 | | 2.21 | 4.6 | | | | | | |

| d3p | d3vitd | d3pth | d3ealkp | d4ca | d4alb | d4mg | d4p | d4vitd | d4pth | d4ealkp | d5ca | d5alb | d5mg | d5p | d5vitd | d5pth | d5ealkp | d6ca | d6alb | d6mg | d6p | d6vitd | d6pth | d6ealkp | d7ca | d7alb | d7mg |
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| | | | | | | | | | | | | | | | | | | 7.16 | | 2.03 | 5.1 | | | | | | |
| | | | | 8 | | 1.9 | 2.7 | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 8.9 | | 1.64 | 3 | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.14 | | 1.75 | 3.4 | | | | | | |
| | | | | | | | | | | | 9.06 | | 2.58 | 3.4 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 8.7 | | 2.07 | 3.4 | | | | | | |
| 4 | | | | 7.6 | | | | | | | | | | | | | | 9.1 | | 1.83 | 4.9 | | | | | | |
| | | | | 7.9 | | 1.29 | 5.6 | | | | | | | | | | | | | | | | | | | | |
| | | | | 8.7 | | 2.06 | 4.1 | | | | | | | | | | | | | | | | | | | | |
| | | | | 9.9 | | 1.76 | 3 | | | | | | | | | | | | | | | | | | 10.6 | 3.8 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | 8.5 | | 2.3 | 3.2 | | | | | | | | | | | | | | | | | | | | |
| | | | | 9.66 | | 2.17 | 3.5 | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.3 | | 1.8 | 4.3 | | | | | | |
| 3.2 | | | | | | | | | | | | | | | | | | 8.9 | | 1.8 | 3 | | | | | | |
| | | | | 7.7 | | 1.77 | 4.9 | | | | | | | | | | | | | | | | | | | | |
| 4.2 | | | | 7.04 | | 1.58 | 4.7 | | | | | | | | | | | 7.5 | | 1.85 | 5 | | | | | | |
| | | | | | | | | | | | | | | | | | | 8.8 | | 1.97 | 3.2 | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.12 | | 1.74 | 5.1 | | | | | | |
| | | | | | | | | | | | | | | | | | | 7.4 | | 1.55 | 6.1 | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.5 | | 1.91 | 6.1 | | | | | | |
| | | | | 10.3 | | 2.04 | 4.6 | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.2 | | 1.47 | 3.6 | | | | | | |
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| 3.6 | | | | | | | | | | | | | | | | | | 8.9 | | 1.49 | 5.3 | | | | | | |
| | | | | | | | | | | | | | | | | | | 9.4 | | 1.99 | 3.4 | | | | | | |
| | | | | | | | | | | | | | | | | | | 8.2 | | 1.31 | 4 | | | | | | |
| | | | | 9.5 | | 1.47 | 3.9 | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 7.2 | | 1.85 | 6.2 | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | 8.6 | | 1.54 |
| | | | | | | | | | | | 9.3 | | 2.74 | 6.8 | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | 8.6 | | 1.94 | 3.7 | | | | | | |
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| 5.8 | | | | | | | | | | | 8.2 | | 1.9 | 5.9 | | | | 8.6 | | 1.63 | 4.8 | | | | | | |
| | | | | 7.6 | | 2.09 | 4.5 | | 1.8 | | | | | | | | | | | | | | | | 8.3 | | 1.7 |
| | | | | | | | | | | | | | | | | | | 9.8 | | 1.91 | 3.8 | | | | | | |
| | | | | 8.9 | | 1.7 | 3.6 | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | 9 | | 1.88 | 6.4 | | | | | | |
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| d7p | d7vitd | d7pth | d7ealkp | d8ca | d8alb | d8mg | d8p | d8vitd | d8pth | d8ealkp | d9ca | d9alb | d9mg | d9p | d9vitd | d9pth | d9ealkp | d15ca | d15alb | d15mg | d15p | d15vitd | d15pth | d15ealkp | pthrep | d1cal | caldose1 |
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| 3.2 | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | 1 |
| | | | | 9.5 | | 2.01 | 3.8 | | | | | | | | | | | | | | | | | | | 1 | 1 |
| | | | | 9.4 | | 1.69 | 3.6 | | | | | | | | | | | | | | | | | | | 1 | 1 |
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| | | | | 9.3 | | 1.92 | 5.9 | | | | | | | | | | | | | | | | | | | 1 | 1 |
| | | | | 8.7 | | 1.78 | 4.7 | | | | | | | | | | | | | | | | | | 11 | 1 | 1 |
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| 3.8 | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
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| 5.1 | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | 1 |
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| | | | | 11.6 | | 1.49 | 6.1 | | | | | | | | | | | | | | | | | | | 1 | 1 |
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| | | | | 9.4 | | 2 | 4 | | | | | | | | | | | | | | | | | | | 1 | 1 |
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| | | | | 9.6 | | 1.64 | 3.3 | | | | | | | | | | | | | | | | | | | 1 | 1 |
| | | | | 9.7 | | 1.6 | 3.8 | | | | | | | | | | | | | | | | | | | 1 | 1 |
| | | | | 8.5 | | 1.85 | 4.2 | | | | | | | | | | | | | | | | | | | 1 | 1 |
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| al | caldose2 | d3cal | caldose3 | d4cal | caldose4 | d5cal | caldose5 | d6cal | caldose6 | d7cal | caldose7 | d8cal | caldose8 | d9cal | caldose9 | d15cal | caldose15 | ivreq | ivyes | d1vitd1 | vitddose1 | d2vitd1 | vitddose2 | d3vitd1 | vitddose3 | d4vitd1 | vitddose4 |
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| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 2 | | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 |
| 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 1 | 0.5 | 1 | 0.5 |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | 2 | | 2 | | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | | 2 | | 2 | | 2 | | 2 | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | | | | | 2 | | 2 | | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 |
| 1 | 1 | | | | | | | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | | | | | | | | | 2 | | 1 | 0.5 | 1 | 0.5 | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 2 | | 1 | 0.5 | 1 | 0.5 | 1 | 1 | 1 | 1 |
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| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | | | | | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | | | | | | | | | 2 | | 1 | 0.5 | 1 | 0.5 | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 2 | | 2 | | | | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | | |
| 1 | 2 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 60 | 2 | | 2 | | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 60 | 2 | | 2 | | 2 | | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | | | | | | | | | 2 | | 2 | | 2 | | 2 | | 2 | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | | | | | | | | |

| d5vitd1 | vitddose5 | d6vitd1 | vitddose6 | d7vitd1 | vitddose7 | d8vitd1 | vitddose8 | d9vitd1 | vitddose9 | d15vitd1 | vitddose15 | mgreq | mgregys | mgdose | diag | ifother | tumsize | focal | cent | etc | lvi | capinv | limbnod | lympys | reexp |
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| 1 | 0.5 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | | 1 | | 3.5 | 1 | | 2 | | 1 | 1 | 2 | 2 |
| 2 | | 2 | | 2 | | 2 | | 2 | | 2 | | 2 | | | 7 | | 3 | 2 | | 1 | | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 5 | | | | | | | | | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 7 | | 4.5 | 1 | | 1 | | 1 | 2 | | 2 |
| 2 | | | | | | | | | | | | 2 | | | 7 | | 1.7 | 2 | | 2 | | 2 | 1 | 2 | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 12 | | 4.2 | 1 | | 2 | | 2 | 2 | | 2 |
| 1 | 0.5 | 1 | 0.5 | | | | | | | | | 2 | | | 1 | | 4.3 | 2 | | 2 | 1 | 2 | 2 | | 2 |
| | | | | | | | | | | | | 2 | | | 4 | | 3.5 | 1 | | 2 | | 2 | 1 | 2 | 2 |
| | | | | | | | | | | | | 2 | | | 7 | | 0.2 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| | | | | | | | | | | | | 2 | | | 6 | | | | | | | | | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 5 | | | | | | | | | | 2 |
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| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 6 | 2 | | 1 | | 1 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 14 | | 4.7 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 4 | | 4.6 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | | | 1 | 2 | 6 | 1 | | 1.6 | 1 | | 1 | 2 | 1 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 0.4 | 1 | | 1 | 2 | 1 | 2 | | 2 |
| 1 | 0.5 | 1 | 0.5 | | | | | | | | | 2 | | | 9 | | 2.2 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 14 | | 3 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 8 | | 1.2 | 1 | | 2 | | 2 | 2 | | 2 |
| | | | | | | | | | | | | 2 | | | 8 | | 4.5 | 2 | | 2 | 1 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 1.1 | 2 | | 2 | 2 | 2 | 1 | 2 | 2 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | | 15 | | | | | | | | | | 2 |
| 2 | | 2 | | 2 | | | | | | | | 2 | | | 2 | | 1.3 | 1 | | 2 | | 2 | 2 | | 2 |
| 2 | | 2 | | 2 | | | | | | | | 2 | | | 5 | | | | | | | | | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 6.5 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 2 | | 7.5 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 1.4 | 2 | | 1 | 2 | 1 | 1 | 1 | 2 |
| | | | | | | | | | | | | 2 | | | 2 | | 1.8 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 14 | | | 1 | | 2 | 1 | 1 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 14 | | 1.5 | 1 | | 2 | 2 | 2 | 1 | 3 | 2 |
| 2 | | 2 | | 2 | | | | | | | | 2 | | | 6 | | | | | | | | | | 2 |
| 2 | | | | | | | | | | | | 2 | | | 8 | | 2.9 | 2 | | 2 | 2 | 1 | 2 | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 10 | | 0.7 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 7 | | 5 | 2 | | 2 | 2 | 2 | 1 | 1 | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 5 | | | | | | | | | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 2 | | 5.5 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 2 | | 3.5 | 1 | | 2 | 2 | 2 | 1 | 1 | 2 |
| | | | | | | | | | | | | 2 | | | 15 | | | | | | | | | | 2 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | | 3.5 | 2 | | 1 | 1 | 1 | 1 | 2 | 2 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | | 5 | | | | | | | | | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 9 | | 0.5 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| | | | | | | | | | | | | 2 | | | 8 | | 2.5 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 1 | | 5 | 1 | | 1 | 1 | 1 | 1 | 1 | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | | | | | | | | | | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 7 | | 3.5 | 2 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | 2 | | 2 | | | | | | 2 | | | 10 | | 0.5 | 1 | | 2 | 2 | 2 | 2 | | 2 |
| 2 | | 2 | | | | | | | | | | 2 | | | 7 | | 3 | 2 | | 2 | 2 | 2 | 1 | 2 | 2 |
| | | | | | | | | | | | | 2 | | | 2 | | 3.5 | 2 | | 2 | 2 | 2 | 1 | 2 | 2 |